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SERUM PROTEIN CONCENTRATION AS A GUIDE TO THE TREATMENT OF DEHYDRATION IN DIARRHEAL DISEASES

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ALTHOUGH the diarrheal diseases of infants are no longer responsible for as many deaths as formerly, the difficulties encountered in the management of severe cases are often greater than one would expect from the present day knowledge concerning the subject. To some degree, these difficulties arise because of the impossibility of applying this knowledge in a practical way to small infants. In adult patients a recorded urine and stool volume and frequent estimations of the chloride and carbon dioxide combining power of the blood are easily obtainable guides to progress and therapy; but in infants such data are rarely obtainable in reliable form. The pediatrician is often left to depend on his clinical acumen and judgment for the help which objective laboratory guides might otherwise give. The present work was undertaken to ascertain the value of a simple determination of serum protein concentration in the practical management of dehydration, which so often constitutes the major aspect of diarrheal diseases.

While the importance of a low serum protein concentration is well recognized in association with edema, the reverse, namely a high protein level in dehydration, has received less attention. The work of Starling[1] offers a fundamental physiologic basis for understanding both of these conditions. Schmidt[2] in 1850 appears to have been the first actually to measure the protein concentration of the serum of patients suffering from fluid loss, and he obtained values of 10 to 11 per cent. In 1909, Reiss[3] studied the protein content of the blood serum, using the refractometric method, in relation to weight changes of infants having various diseases, including diarrhea and vomiting. Schloss,[4] and Marriott[5] also found the serum protein level to be a helpful guide in the treatment of dehydration, and the work to be reported below is an outgrowth of the studies by Schloss and collaborators, most of which have not as yet been published.

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METHODS

The present study was made on a group of 130 infants under 2 years of age who were admitted to the hospital wards because of problems in fluid regulation. A majority were classed as dysentery or nonspecific summer diarrhea, but in a few cases the fluid deficit was caused by other conditions, such as pyloric stenosis, inanition fever of the newborn infant, and diarrhea associated with acute respiratory infections. The correlation of day to day changes in the general condition of the infants with corresponding values for serum protein concentration served as the basis of the study. In part of the group hemoglobin estimations were also made as an additional index of blood concentration and dilution. While it was fully appreciated that fluid regulation constituted only one aspect of the total problem, the present work was confined to this phase which presented one of the most important aspects of therapy.

Since the purpose of the study was to obtain information concerning the practical usefulness of serum protein determinations in the treatment of dehydration, the methods employed were necessarily simple. Blood was obtained from finger pricks and collected in capillary tubes. After centrifugation, the portion containing the serum was broken off and used for analysis. During the first years of the work, the protein concentration was determined by the refractometric method using the factor of Neuhausen and Rioch.[6] While the limitations of the method were fully appreciated, no other procedure was available at the time which was suitable for rapid and frequent determinations on small infants in whom repeated venepunctures were impossible. Furthermore, since the major source of error in this method results from unsuspected shifts in the proportion of albumin to globulin, it seemed unlikely that significant changes in this ratio would occur in acute dehydration, or during the course of several days of treatment. Occasional checks by macromethods, and the later use of the specific gravity method of Kagan[7] have confirmed this assumption and demonstrated a satisfactory correlation between the methods employed.* In individual patients the relative changes in serum protein concentration during the course of fluid administration have been consistent and reliable regardless of the method employed.

In attempting to correlate serum protein values with degrees of dehydration, we were faced with a difficulty, common to many clinical conditions, of finding disagreement among the physicians examining the children as to the significance of the physical signs present on admission. Therefore, to obtain a reasonably accurate estimation of the state of a child on admission, each case was reviewed in retrospect considering (a) the course of the child's response to fluid in addition to (b) the clinical judgment of the examining physicians and (c) the history, in that order of importance. If, for example, the child showed a large gain in weight

*The recent introduction of the photoelectric colorimeter has added another method for microestimation of the total serum proteins.

TABLE I

DATA FOR NORMAL INFANTS

INVESTIGATOR	METHOD	PREMATURE INFANTS				INFANTS: 0-3 MONTHS				INFANTS: 3 MO.-2 YR.			
		NO. OF CASES	SERUM PROTEIN (%)			NO. OF CASES	SERUM PROTEIN (%)			NO. OF CASES	SERUM PROTEIN (%)		
			AV.	RANGE OF ⅔ OF DATA	EXTREMES		AV.	RANGE OF ⅔ OF DATA	EXTREMES		AV.	RANGE OF ⅔ OF DATA	EXTREMES
Darrow and Carey[8]	Micro-Kjeldahl	27	4.9	4.4-5.4	3.9-6.9	20	5.5	5.1-5.6	4.6-6.9	14	6.3	6.1-6.6	5.9-6.9
Utheim[9]	Refractometer*	19	4.6	4.1-5.1	3.7-5.4	17	5.9	5.6-6.1	5.4-6.3	17	6.5	5.9-7.0	5.0-7.8
Dodd and Minot[10]	Micro-Kjeldahl					16	5.5	5.2-5.9	4.1-6.7	34	6.2	5.8-6.6	5.2-7.2
Bakwin[11]	Refractometer†					41	5.8	5.4-6.2	4.8-6.4				
Rennie[12]	Kjeldahl									22	7.1	6.6-7.6	6.0-8.0
Present authors	Refractometer and specific gravity[7]	5	4.5	4.4-4.6	4.1-5.1	22	5.5	5.2-5.7	4.6-6.7	44	6.3	6.1-6.8	5.1-7.4
Av. value			4.7				5.7				6.5		

*Recalculated according to the factor of Neuhausen and Rioch.[6]

†Data selected for the fifth, sixth, seventh days of life, recalculated according to the factor of Neuhausen and Rioch.[6]

in the first three days while fluid was being administered and maintained that weight gain after fluid was discontinued, it would be reasonable to suppose that the child had had a fluid deficit on admission which was relieved by treatment. If, in addition, this child had the classical clinical signs of dehydration and a history of severe diarrhea, vomiting, and weight loss, such a child would be diagnosed as having a "severe" degree of dehydration. On the other hand, if such an initial weight gain were lost when fluid was discontinued although the child continued to improve, then there could have been little need of fluid on admission. Children with such a course were occasionally found to have been described as severely dehydrated on admission. However, if their course was that of a "slight" dehydration, they were classified as such regardless of the initial impression. Intermediate groups of children were classified as having a "moderate" degree of dehydration. We realized that this method of classification was subject to the usual errors of judgment, but it seemed, nevertheless, that such an approach would give as correct a clinical classification as was possible with the data available.

NORMAL VALUES

It is well known that the normal concentration of serum proteins is lower in infants than in adults. Although the reports available in the literature are based on a variety of methods, the data presented in Table I show the results to be surprisingly consistent. The average normal levels of 4.7 per cent for premature infants, 5.7 per cent for full-term infants up to 3 months of age, and 6.5 per cent for children from 3 months to 2 years offer a basis for comparison with the findings in dehydrated infants discussed below. While it is true that the variations encountered among the so-called "normal" infants are somewhat large, in such sample groups the effects of technical errors, diet, fluid balance, liver function, etc., will be roughly balanced. In the day to day course of an individual child, the relative changes are more important than average values.

RESULTS

In seventy-six infants it was possible to compare the level of the serum proteins found on admission to the hospital with the degree of dehydration, this last being estimated in retrospect as discussed above. As will be seen in Table II, the average level of serum proteins was 8.3 per cent in infants considered to be severely dehydrated, 7.7 per cent in cases of moderate dehydration, and 6.9 where the fluid deficit was thought to

TABLE II

DEHYDRATION (FINAL ESTIMATE)	NO. OF CASES	SERUM PROTEIN (%)		
		AV.	RANGE OF $\frac{2}{3}$ OF DATA	EXTREMES
Slight	27	6.9	6.2-7.5	5.7-8.2
Moderate	16	7.7	7.1-8.4	6.2-9.0
Severe	33	8.3	7.5-8.9	6.9-10.3

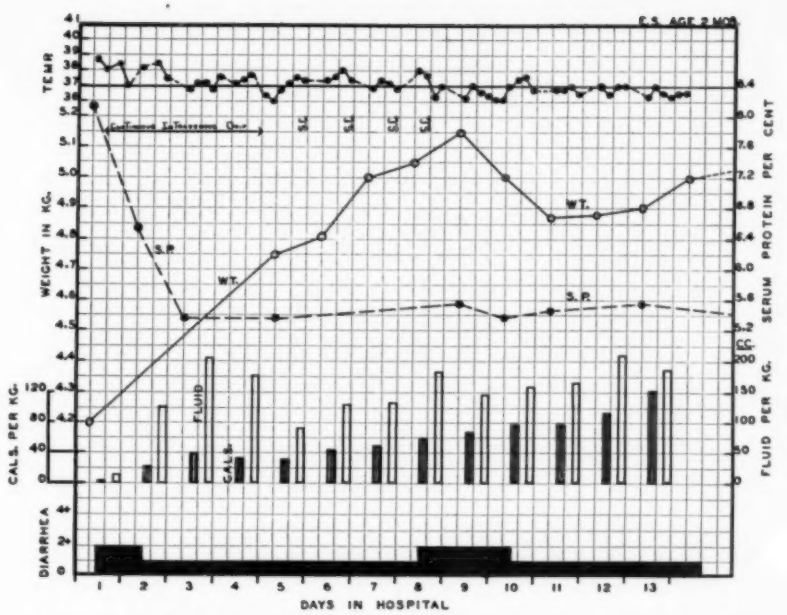

Fig. 1.—Chart showing decrease in serum protein concentration corresponding to the increase in weight of a severely dehydrated infant following administration of parenteral fluids. S. C. = subcutaneous infusion of saline solution. S. P. = serum protein concentration.

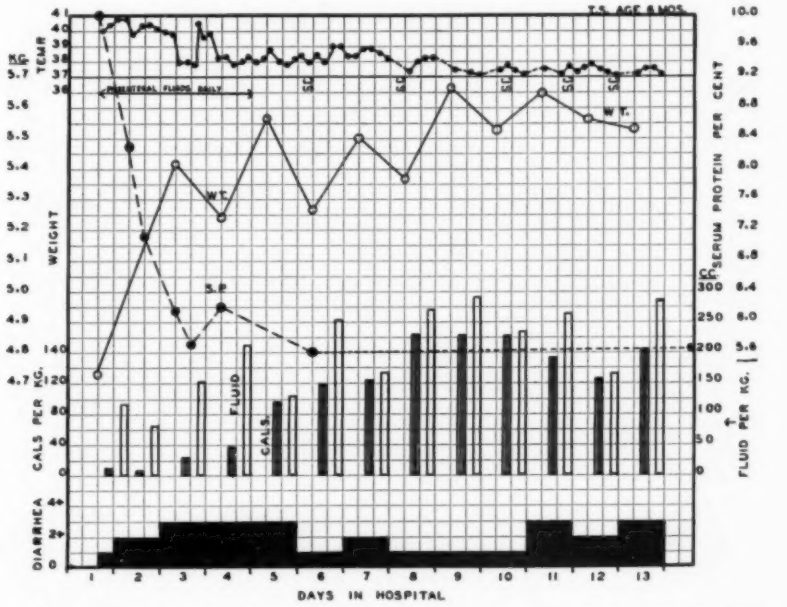

Fig. 2.—Chart showing inverse relationship between serum protein concentration and weight in a severely dehydrated infant receiving parenteral fluids. S. C. = subcutaneous infusion of saline solution. S. P. = serum protein concentration.

be slight. The average normal value for such a group varying in age from 1 to 24 months would be approximately 6.2 per cent. Thus in a general way the concentration of serum protein reflected the degree of dehydration as estimated by other means.

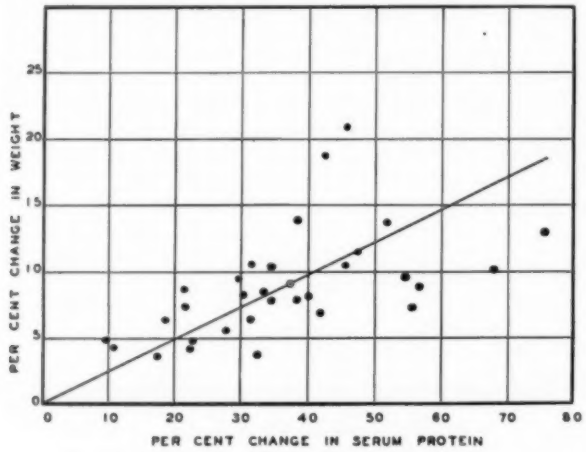

Fig. 3.—Chart showing relationship between the weight gain and the decrease in concentration of serum protein during recovery from dehydration in thirty-one infants with diarrheal diseases. The percentages are based on the hydrated weight and protein level. The line is drawn through a point which represents the arithmetic average.

The relationship is demonstrated more clearly in the day to day changes in weight and serum protein level during active treatment of severe dehydration. Figs. 1 and 2 are examples taken from the records of two of the ninety infants from whom such data were obtained. Almost without exception, clinical improvement was accompanied by an increase in weight and a decrease in serum protein concentration toward normal. The association of increasing weight with decreasing serum protein concentration, and vice versa, has been so consistent throughout the study that an attempt was made in Fig. 3 to see if such an association were more than incidental. When the percentage gain in weight is plotted against the percentage fall in serum protein concentration, it will be seen that a general relationship is suggested, the average values representing an increase of 12.5 per cent in weight for a corresponding 50 per cent decrease in protein concentration. While the data are insufficient to establish a definite correlation, they suggest that for every 1 Gm. per cent increase in serum proteins, the body has lost approximately 4 to 6 per cent in weight.*

OVERTREATMENT

To recognize the presence of acute dehydration in a small infant with diarrheal disease is seldom difficult. The classical signs of inelastic

*Example. A change in serum protein concentration from 7.0 to 6.0 Gm. per cent represents a 16.6 per cent decrease. This, according to the average line on Fig. 3, corresponds to a gain of 4.2 per cent in weight.

skin, sunken eyeballs, depressed fontanel, and dry mucous membranes are well known to every physician. But after the initial crisis has passed and fluids are being administered, the question of how much to give and when to stop is by no means so simple. Usually the decision is made on the basis of the clinical signs at the time and the estimated severity of the fluid loss. Since both are dependent on personal experience and judgment, it is not surprising that errors of both overtreatment and undertreatment should occasionally result. In the present study, seventeen infants showed evidences of overtreatment as judged by excessive weight gain which in four instances was associated with edema. The records of these infants were studied to determine, if possible, the difficulties responsible for the unnecessary administration of fluids. Although such decisions cannot be made with scientific accuracy, in general it seemed justifiable to divide the cases into two parts. In one the degree of dehydration appeared in retrospect to be less than that on which the fluid therapy was planned. In the other, the degree of dehydration was correctly appreciated, but unnecessarily large amounts of fluid were given. Tables III A and III B present the data obtained on these infants.

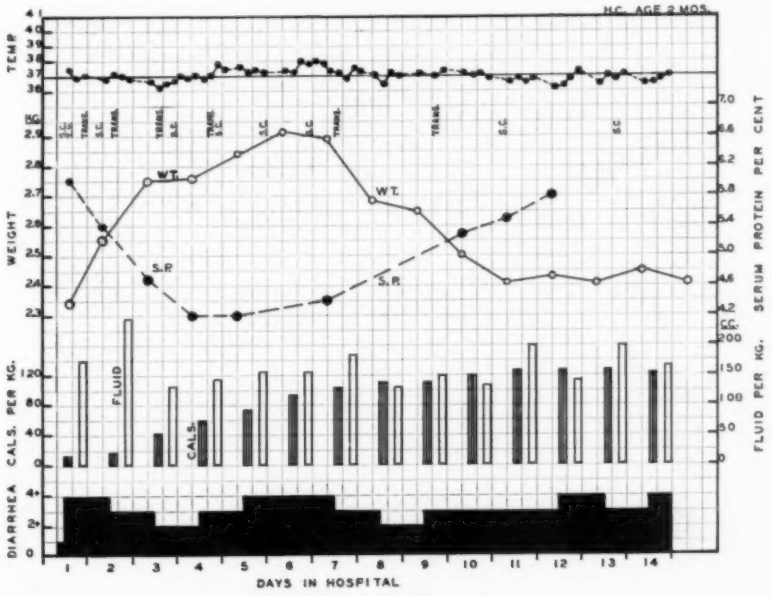

Fig. 4.—Chart showing changes in weight and serum protein concentration of an infant having mild dysentery, who was erroneously treated for supposed dehydration.

An example of the infants in whom overtreatment appeared to result from a misinterpretation of clinical signs is shown in Fig. 4. On admission this infant was considered to be extremely dehydrated on the basis of history, inelastic skin, and sunken fontanel. However, at this time the serum protein concentration was found to be 6.0 per cent, a

TABLE III A

OVERTREATMENT DUE TO ERROR IN EVALUATING CLINICAL SIGNS

PATIENT	AGE (MO.)	DIAGNOSIS	NUTRITION	DEHYDRATION ON ADMISSION		SERUM PROTEIN (%)			WEIGHT (GM.)			EDEMA	TREATMENT
				CLINICAL	IN RETROSPECT	ON ADMISSION	LOWEST	BEGINNING CONVALESCENCE	ADMISSION	MAXIMUM	BEGINNING CONVALESCENCE		
H. C.	1.5	Dysentery	Poor	Severe	0	6.0	4.2	5.8	2,340	2,910	2,410	Puffy eyes	S. C., I. V.
T. S.	7	Diarrhea*	Very poor	Severe	Slight	6.3	4.1	5.1	4,360	5,470	4,440	0	S. C., I. V.
J. S.	2	Diarrhea	Obese	Slight	Slight	7.0	5.0	6.0	5,050	5,680	5,200	0	S. C.
C. C.	1	Diarrhea	Very poor	Moderate	0	6.8	5.1		3,050	3,290	2,930	0	S. C., continuous I. V.
E. J.	4	Diarrhea	Poor	Slight	0	6.2	4.4	6.3	4,370	4,880	4,360	0	S. C.
J. J.	1	Diarrhea†	Very poor	Severe	Slight		4.5	5.1	2,460	2,950	2,700	0	Continuous I. V.
R. G.	13	Typhoid	Poor	Severe	0	5.7	4.3		7,520	8,280	7,700	0	S. C.
D. M.	7	Dysentery	Poor	Slight	0	5.5	3.8	6.2	5,240	5,840	5,500	0	S. C.
N. B.	14	Diarrhea‡	Fair	Slight	0	7.3	5.9	6.8	7,480	7,900	7,380	0	S. C.

*Nonspecific diarrhea in all cases unless otherwise stated.
†Epidemic diarrhea of the newborn infant.
‡Diarrhea and pyelitis.

TABLE III B

OVERTREATMENT DUE TO EXCESSIVE ADMINISTRATION OF FLUIDS

CASE	AGE (MO.)	DIAGNOSIS	NUTRITION	DEHYDRATION ON ADMISSION		SERUM PROTEINS (%)			WEIGHT (GM.)			EDEMA	TREATMENT
				CLINICAL	IN RETROSPECT	ON ADMISSION	LOWEST	BEGINNING CONVALESCENCE	ON ADMISSION	MAXIMUM	BEGINNING CONVALESCENCE		
J. B.	2	Diarrhea*	Very poor	Severe	Severe	7.5	4.2	5.3	3,180	3,780	3,410	0	Continuous I. V.
E. M.	3	Diarrhea	Very poor	Moderate	Severe	7.9	5.6		2,230	2,830	2,500	0	Continuous I. V.
J. N.	7	Dysentery	Fair	Moderate	Moderate		4.7	5.9	5,940	6,860	6,300	0	S. C.
G. D.	20	Dysentery	Very good	0	0	5.4	4.1	5.9	11,790	12,490	11,840	Puffy eyes	S. C.
P. H.	6	Dysentery	Good	Slight	Slight	6.6	5.1	5.9	5,680	6,350	5,770	Puffy eyes	S. C.
H. B.	4	Dysentery	Fair	Severe	Severe	7.4	5.6	6.1	5,590	6,590	5,450	Slight edema	S. C., I. V., I. P.
M. P.	7	Dysentery	Good	Slight	Slight	7.4	5.3	5.5	6,200	6,800	6,400	0	S. C.
D. M.	4	Diarrhea	Good	Slight	Moderate	6.8	5.7	6.6	5,660	6,380	5,840	0	Continuous I. V.

*Nonspecific diarrhea, in all cases, unless otherwise stated.

figure representing the upper range of normal for a child of this age. Following repeated subcutaneous infusions of saline solution and transfusions he gained 25 per cent in weight and showed moderate edema of the eyes and scalp with a serum protein of 4.2 per cent. Upon reducing the amount of parenteral fluid, the weight gradually fell to 70 Gm. above the admission level accompanied by a return of the serum protein level to 5.8 per cent and satisfactory improvement in the general condition. As judged by the course of the weight and serum protein concentration it appears that, in spite of clinical appearances of dehydration, little if any true fluid deficit existed, and that treatment was unnecessarily vigorous. It seems probable in this case that extreme malnutrition presented signs which were mistaken for dehydration.

From an analysis of the group of cases (Table III A) which the above infant illustrates, it has seemed likely that errors arise not infrequently from a misinterpretation of the clinical state. While the classical signs of inelastic skin, sunken eyeballs and fontanel, and dry mucous membranes are obvious and clear-cut in infants who are severely dehydrated, they are by no means specific when considered individually. For example, severe malnutrition or recent marked loss of weight may so deplete the subcutaneous fat as to leave the skin loose, wrinkled, and *apparently* inelastic. Such a weight loss may also reduce the fat of the eye sockets, giving the eyeballs the sunken appearance of acute dehydration. The presence of a depressed fontanel and dry mucous membranes, even if added to the above picture, may only indicate a relatively mild fluid deficit which has gone far enough to shift fluid from the extracellular region but has not yet affected the blood volume to an appreciable degree. Such a state is seen in the dehydration accompanying starvation. On the other hand, difficulty in judging the state of dehydration occurs with obese babies in whom subcutaneous fat prevents accurate appreciation of the degree of elasticity of the skin, and also with those infants to whom repeated subcutaneous infusions have been given. Unless these possibilities are kept in mind constantly or some criterion of dehydration is available which is free from such errors, it is not surprising that inefficient treatment should occasionally result.

In view of the fact that the difficulties enumerated above are encountered most commonly in malnourished and underfed infants, it is interesting to note that in the group in whom overtreatment was thought to result from incorrect evaluation of the state of dehydration, all but one were poorly nourished; the exception was an obese infant. It should also be noted that in this series of infants, judging from the level of serum protein concentration during convalescence, the initial serum protein was essentially normal in spite of their undernutrition.[10] It would seem, therefore, that serum protein data were helpful in distinguishing true dehydration from those conditions in which the clinical signs were indefinite or confusing.

The second group of overtreated infants (Table III B) in whom the degree of dehydration appears to have been satisfactorily evaluated but to whom unnecessarily large amounts of fluid were given is also of interest. Here a knowledge of the changes in serum protein levels offers useful information to the physician. A fall of serum protein concentration to low levels enables the fluid administration to be reduced or discontinued before a tendency toward edema develops to complicate the picture.

While it is no doubt true that complications and dangers of overtreatment are of less importance than those of undertreatment, the goal of all therapeutics should be toward exactness and precision. The pain, discomfort, and lack of rest resulting from the unnecessary administration of parenteral fluid may at times interfere with recovery, and the same may also be said when edema, either occult or visible, develops. Through the use of serum protein data in conjunction with clinical judgment, it should be possible to reduce the incidence of overtreatment and to make therapy in the diarrheal diseases more specific.

UNDERTREATMENT

Although a great majority of the children studied made an excellent recovery from both the acute dehydration and the underlying disease, seven infants were followed who failed to respond to routine treatment and, with one exception, grew steadily worse, and died. In all of those patients dehydration persisted as a major problem. Since such experiences are encountered in all pediatric clinics, it is this group, perhaps more than all others, which needs careful study to determine the cause of the therapeutic failures.

In Table IV are presented the pertinent data concerning the undertreated infants of this group. It will be seen that in all patients clinical dehydration and high levels of serum protein persisted in spite of treatment that was considered by the clinicians at the time to be adequate. However, in retrospect, it appears that in four of them fluid intake was probably too low, while in the other three the body was unable to utilize the fluid which was given in large amounts. In one case, severe inanition added difficulties to the diagnosis and contributed to the death. In another, low-grade pneumonia complicated the picture. In five patients of the group acidosis, usually recognized too late, was the major complication.

Fig. 5 illustrates, in a patient who recovered, the contrast between the initial seven days of unsatisfactory treatment and the succeeding week of convalescence. It will be seen that, in spite of 100 to 160 c.c. of fluid per kilogram of body weight given by the usual parenteral routes she remained clinically dehydrated; serum proteins, although falling, continued above normal. The temperature gradually rose without evident cause, and the general condition became critical. Following a change to the continuous intravenous method of fluid admin-

TABLE IV

UNDERTREATMENT

CASE	AGE (MO.)	DIAGNOSIS	ADMISSION		LATER		DIARRHEA	FLUIDS GIVEN	COMPLICATIONS	OUTCOME	TREATMENT
			DEHYDRATION	SERUM PROTEIN (%)	DEHYDRATION	SERUM PROTEIN (%)					
V. S.	2	Diarrhea*	Severe	8.5	Moderate	7.0	Moderate	Moderate	0	Recovered	I. V., S. C., continuous I. V.
L. T.	2	Diarrhea	Severe	8.5	Slight	7.8	Severe	Low	Malnutrition	Died on eighth day	I. V., S. C., I. P.
M. R.	1	Diarrhea	Severe	7.8	Moderate	7.2	Severe	Low	Acidosis	Died on seventh day	I. V., S. C.
G. S.	5	Diarrhea	Severe		Moderate	7.7	Moderate	Low	Acidosis and pneumonia	Died on fifth day	I. V., S. C.
I. F.	7	Dysentery	Severe	8.6	Moderate	7.8	Severe	High	Acidosis	Died on eighth day	S. C.
E. B.	8	Diarrhea	Severe	9.5	Moderate	7.2	Severe	High	Acidosis	Died on sixth day	Continuous I. V., S. C.
L. J.	16	Dysentery	Severe	8.4	Moderate	7.2	Severe	High	Acidosis	Died on fourteenth day	Continuous I. V.

*Nonspecific diarrhea, unless otherwise stated.

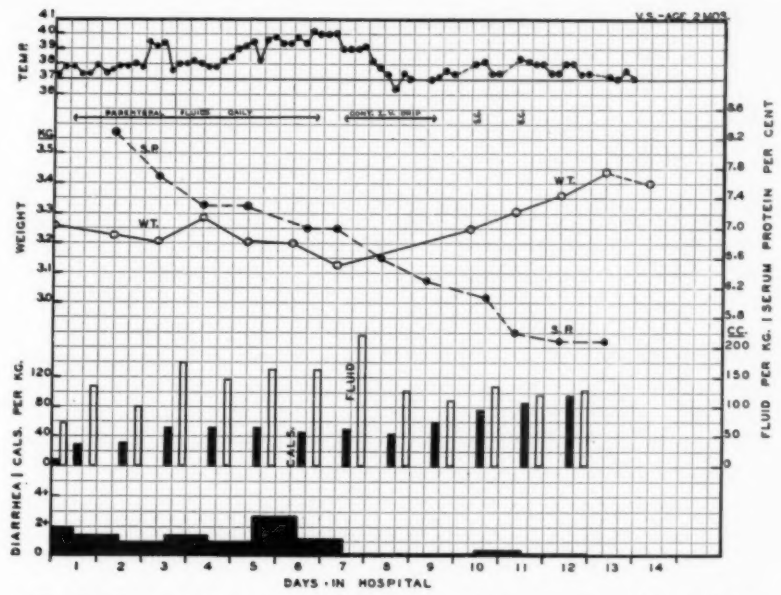

Fig. 5.—Chart showing relationship between weight and serum protein level during a week of inadequate treatment, followed by a week in which fluid administration brought about rapid recovery.

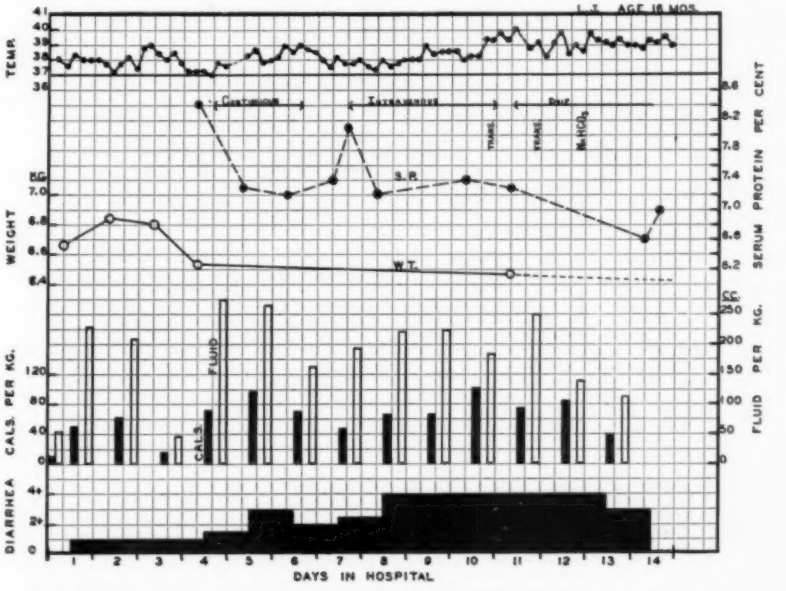

Fig. 6.—Chart showing constantly high levels of serum protein in an infant whose clinical dehydration was not improved in spite of large volumes of fluid given through a continuous intravenous drip. The treatment of acidosis, which was discovered late in the course of the disease, resulted in temporary improvement.

istration, the serum protein concentration fell rapidly to normal and the child made an uneventful recovery. This case illustrates the value of knowledge of serum protein levels as a guide to the adequacy of the treatment.

Fig. 6 presents the data from a sixteen-month-old child with Flexner dysentery in whom an unsuspected acidosis complicated the picture. Although appearing only moderately ill on admission and taking large amounts of fluid by mouth during the first three days, he failed to improve and dehydration with a high serum protein level persisted. During the succeeding eleven days he received large amounts of 5 per cent glucose in half strength physiologic saline solution by continuous intravenous drip, voided as much as 800 to 950 c.c. a day, but remained clinically dehydrated with high serum protein levels and became steadily worse. Such an anomalous state of dehydration in the presence of adequate fluid intake and urine output suggested some interference with tissue utilization of the fluid. In this case the condition appeared to depend on an unsuspected acidosis, probably present from the time of admission. Toward the end, the carbon dioxide combining power of the blood was found to be 30 volumes per cent, and the administration of $NaHCO_3$ to correct this was followed by temporary improvement of hydration which was reflected both in improved texture of the skin and in a fall in serum protein concentration. Death, however, occurred thirty-six hours later.

In this case there appears to be a good correlation between serum protein levels and the state of hydration. The case also illustrates the fact that a state of acidosis, even though it is not severe enough to be suspected clinically, may interfere with proper hydration in spite of the administration of large amounts of fluid.

TRANSFUSIONS

During the course of these observations, experiences were encountered which suggested that the giving of large and repeated transfusions to infants with diarrheal diseases might not be without danger. Apart from the ordinary febrile, anaphylactic, and hemolytic transfusion reactions, a small group of infants following transfusions appeared to show a marked rise in serum proteins accompanied by dehydration. One of these children, aged 3 months and weighing 3,500 Gm., was given parenteral fluid and a whole blood transfusion of 20 c.c. per kilogram of body weight as initial treatment for a mild diarrhea. She reacted well with gain in weight, a fall in serum proteins to a normal level (6.3 per cent), and a rise in hemoglobin to 13 Gm. (90 per cent). A markedly flushed skin during the following twenty-four hours suggested an increase in the circulating blood volume. Although doing well, forty-eight hours later she was given another whole blood transfusion of 20 c.c. per kilogram as a general tonic measure. Following this she had an immediate circulatory collapse with cyanosis and vomit-

ing. In the succeeding two days she lost weight and became dehydrated, and the serum proteins rose from 6.3 to 8.3 per cent. In spite of fluid therapy and stimulants she became steadily worse, remained dehydrated, and died seventy-two hours after the second transfusion. Although the data in this case are too meager to allow final conclusions to be drawn, we are inclined to believe from this and other experiences that excessive transfusions may so raise the plasma protein concentration that the balance between fluid intake, tissue hydration, and renal excretion is upset with a resulting shift in water away from the tissues which cannot be corrected by administering parenteral fluids.

DISCUSSION

Dehydration, which has been the main theme of the above discussion, is, of course, only one aspect of the diarrheal diseases. An infection, either enteral or parenteral, sets in motion a disturbance which soon spreads from diarrhea and simple fluid loss to dehydration, renal failure, acidosis, circulatory collapse, hyperpyrexia, and finally to death. While no single phase of the process can rightly be considered apart from the picture as a whole, it may nevertheless be possible to visualize the intensity of individual aspects of the disturbance and to guide therapy accordingly. In the present study, serum protein data have been found useful as an index of the associated dehydration and the need for parenteral fluid administration.

In order that any laboratory procedure may be useful in the bedside care of patients, it is necessary that technical details be reduced to the minimum that is consistent with the needs. To bring this about, the obvious chemical advantages of the Kjeldahl and other methods requiring several cubic centimeters of blood were set aside in the present study for the refractometric and falling drop techniques. These latter procedures can be carried out satisfactorily on blood collected from skin pricks into capillary tubes. From our own observations and from a review of the literature such simplified methods have been found to give results that are sufficiently accurate for clinical purposes. Although hemoglobin concentration has also been utilized as an index of blood concentration and dilution, this has not proved as satisfactory as serum protein level. In addition, any relationship of hemoglobin level to fluid balance must be purely incidental in contrast to plasma protein concentration which is well known to be intimately related to fluid exchange between blood on one side and the tissues and kidney on the other.

In our experience the help derived from a knowledge of serum protein levels during treatment for dehydration has been distinctly valuable in the management of the clinical problems. On admission to the hospital the initial protein concentration aids in estimating the severity of the dehydration, or its existence when clinical signs are doubtful. As the dehydration improves following fluid administration, the serum

protein level falls steadily to normal. Knowing the initial level and the day to day changes during the period of hydration, one can readily recognize a tendency toward overtreatment or undertreatment and adjust therapy accordingly. In this way some of the complications and prolonged convalescence can be avoided.

The importance of daily observations of serum protein concentration needs emphasis for, without a knowledge of the levels during the initial phase of improvement, changes during the later relapses which often prove serious are difficult to evaluate. When such a relapse occurs, it may be too late to obtain all the information necessary to deal with the situation adequately. While it is no doubt true that the average case of infantile dehydration can be treated satisfactorily without observations on the serum protein levels just as diabetes or pneumonia may be treated without a knowledge of blood sugar or blood sulfapyridine level, nevertheless these various laboratory guides are distinctly helpful in making therapy effective and in preventing the complications in certain cases. And since there is no way in which these particular cases can be suspected before the complications arise, it would seem desirable to give all patients the benefit of the knowledge gained by these special procedures.

Theoretically one might expect the variations in serum protein concentration of normal infants to interfere with the interpretation of the levels in cases of dehydration. As Dodd and Minot[10] have pointed out, malnutrition may cause a depletion of blood proteins, and in such patients the serum protein concentration accompanying dehydration may be difficult to recognize. Fortunately, conditions so extreme as to introduce this complication are not encountered frequently, and in our experience this has not constituted an objection to the usefulness of the procedure as a whole. As with all laboratory aids, the results must be used, not as an infallible index, but as a helpful adjunct which makes possible a more accurate appreciation of the clinical state.

The seriousness and frequency of acidosis as a part of the picture of dehydration is everywhere recognized. However, that subclinical acidosis may be associated with continued tissue dehydration even though fluid intake is large and urine output excellent has not been generally appreciated. We have observed several infants in whom acidosis was not severe enough to be detectable by the usual signs of hyperpnea and air hunger, but in whom the complication was first suspected because serum protein level and clinical dehydration did not improve at a time when fluid administration was known to be adequate. In such cases we believe the success of therapy depends on the early recognition and treatment of the underlying acidosis. The investigations of Gamble and Hamilton[13] and of Andrews[14] on the dehydrating effects of acidosis offer an understanding of the physiologic mechanism involved.

In many clinics transfusions, either single or repeated, are considered to be a most important aspect of treatment. Their usefulness must

depend on either an enlarged circulating blood volume, a raised hemoglobin level, or an increased plasma protein concentration. In acute dehydration where reduced blood volume is due to loss of water and is associated with concentration of both cellular and plasma elements saline solution will most readily dilute these constituents and thereby expand the circulating volume. To add more plasma and red cells to a circulation which is already embarrassed by an excessive concentration of these elements has, in our experience, carried with it a certain amount of danger. Once the initial dehydration has been overcome, it seems possible that a transfusion might assist in maintaining a normal circulating volume, but definite evidence of such an effect is rarely seen. In general, we believe that transfusions are indicated in infants with diarrheal diseases whenever anemia, hypoproteinemia, or chronic nutritional disturbances are present and that they are contraindicated in the presence of acute dehydration.

From the study of this group of infants it would seem that the difficulties arising in the treatment of dehydrated babies fall into several groups. In the first place, clinical judgment regarding the need for parenteral fluid may err. These errors, as discussed above, may result from too great reliance on certain clinical signs which are not truly specific for dehydration. Or the confusion may arise from the difficulty or impossibility of estimating from the nurses' bedside notes the amount of fluid lost by vomiting and diarrhea. In the second place, acidosis may be present to a degree sufficient to interfere with hydration and recovery even though no clinical signs of the condition exist. And finally, excessive transfusions may raise the blood volume to such a degree that compensation fails. This is sometimes evident in sudden circulatory collapse; in other cases a hyperproteinemia with dehydration seems to develop which does not respond in the usual way to the administration of fluids. It becomes essential to keep these possibilities constantly in mind in cases in which supposedly adequate treatment does not bring about the expected improvement in clinical state. To appraise the situation correctly we believe a more general use of the simple estimation of serum protein level would be helpful.

Today the diarrheal diseases are less of a menace to small infants than formerly. In part, this is no doubt due to improvement in general sanitation, but at least equally important has been the growth of knowledge concerning fluid regulation and the role which it plays in the nature and treatment of the condition. While it seems probable that the best of available knowledge is adequate to prevent death in almost all instances, in actual practice the difficulties of applying this knowledge to small infants have in the past been almost insurmountable. The present report has described the usefulness of a procedure which is suitable for day to day observations on a major aspect of the condition, viz., dehydration. We believe that it should help in reducing still further the mortality from diarrheal diseases.

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VITAMIN THERAPY IN PROGRESSIVE MUSCULAR DYSTROPHY

Vitamin B_6, Other Factors of the B Complex, and Vitamin E*

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RENEWED interest has been manifested in the etiology and treatment of progressive muscular dystrophy since Blumberg[1] observed muscular changes in rats on diets deficient in vitamin E. Olcott[2] later proved these changes to be dystrophic in nature, and Goettsch and Pappenheimer[3] observed similar dystrophic changes in guinea pigs and rabbits. Bicknell[4] reported improvement in seventeen of eighteen patients with muscular dystrophy who were treated for more than six weeks with ½ oz. of whole wheat germ, twice daily. His findings led him to believe that progressive muscular dystrophy was a deficiency disease. Stone[5] treated five patients with wheat germ oil and in all cases noted definite improvement manifested in "gain in muscle strength, disappearance of fatigue and muscle pain on slight exertion, change in muscle texture and displacement of dystrophic musculature by normally contracting muscle tissue." He also observed that the addition of the vitamin B complex to vitamin E appeared to increase the value of the latter vitamin. Shelden, Butt, and Woltman[6] reported no improvement in eight dystrophic patients who received 45 c.c. of wheat germ oil with each meal in addition to α tocopherol which was administered for periods of three to six weeks in doses of either 100 mg. intramuscularly twice weekly or 50 mg. daily by mouth.

Antopol and Schotland[7] reported considerable improvement in six patients with muscular dystrophy who were given 100 to 500 mg. of vitamin B_6 subcutaneously, weekly in divided doses. Marked and rapid improvement was noted in two instances within one-half hour to three hours after administration of 50 mg. of B_6 intravenously.

Because of the above-mentioned favorable reports, we selected six typical progressive pseudohypertrophic muscular dystrophy patients from a group of thirty for therapy and study. Careful muscle tests were performed at intervals of two to four weeks, and charts of muscle power were kept.

In carrying out this study, 586 individual muscle examinations were made on forty-two muscles or groups of muscles. All tests were made by one worker (L. D. B.) and were recorded according to the standard recommended by Kendall and Kendall[8] (Table I). The number of

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*The authors are indebted to Merck & Co. for the supply of vitamins used in this study.

TABLE I

KEY TO MUSCLE GRADING

PER CENT	SYMBOL	GRADE	TEST
0	0	Zero	No contraction felt in muscle
5	Tr.	Trace	Contraction of muscle felt, but no apparent movement of part
10 20 30	P– P P+	Poor minus Poor Poor plus	A poor muscle moves the part through partial arc of motion with gravity eliminated
40 50 60	F– F F+	Fair minus Fair Fair plus	A fair muscle completes the whole arc of motion against gravity, but may tire after three to six movements. A fair-plus muscle completes the arc of motion against gravity and a minimum amount of resistance
70 80 90	G– G G+	Good minus Good Good plus	A good muscle completes the arc of motion against gravity and a medium amount of resistance several times without showing fatigue, but it tires quickly or is unable to complete the arc of motion when done against a maximum amount of resistance
95 100 (Contracted)	N– N N+	Normal minus Normal Normal plus	A normal muscle completes the arc of motion against gravity and a maximum amount of resistance several times without showing signs of fatigue

tests and the muscles examined are shown in the border columns of Fig. 1. Fig. 1 also illustrates the findings in one patient which are fairly typical of the entire study. In the early examinations we attempted to make complete muscle checks, but as can be seen in Fig. 1, 504 of the tests were made, using ten muscles or groups of muscles; namely, shoulder abductors, hip flexors, and the extensors and flexors of the elbows, wrists, knees, and ankles. These muscles were chosen because of the ease and accuracy with which they could be tested and because of the relatively little fatigue their use brought on, making it possible to carry out the entire examination at one sitting without having the result affected by fatigue or disinterest on the part of the patient. Each muscle test was made without the examiner's referring to the previous test, and since the variations are inconsistent, it is felt that the occasional variations in a few of the muscles are due to either errors in the examiner's judgment or lack of cooperation on the part of the patient, rather than to any real change in the muscle power.

CASE REPORTS

CASE 1.—H. B. (History No. 1547), a white male aged 17 years, with onset at 4 years of age, had first visited the clinic at the age of 7 years. The diagnosis was typical pseudohypertrophic muscular dystrophy, ambulatory.

Treatment was as follows: (1) May 30, 1940, oral B_6, 100 mg. daily for thirty-nine days, with no improvement; (2) July 22, 1940, oral B_6, 100 mg. daily for fourteen days, with no improvement; (3) Aug. 14, 1940, intravenous B_6, 50 mg. daily for twenty-eight days, with no improvement.

CASE 2.—C. W. (History No. 61696), a white female aged 9 years, had had the onset of disease at 3 years of age. The diagnosis was typical pseudohypertrophic muscular dystrophy, ambulatory.

Treatment was as follows: (1) June 10, 1940, intravenous B_6, 100 mg. twice weekly for two weeks, with no improvement; (2) Aug. 17, 1940, intravenous B_6, 50 mg. daily for twenty days, with no improvement; (3) Sept. 13, 1940, oral thiamin chloride 30 mg., riboflavin 15 mg., nicotinic acid 150 mg., B_6 120 mg. (TRN6) daily for thirty-one days, with no improvement.

DUKE HOSPITAL

MUSCULAR DYSTROPHY STUDY

NAME _____ HISTORY NO. 12940

LOCATION Out-Patient-Clinic SERVICE Ped.- Orth.

LEFT							MUSCLE CHART		RIGHT						
TOTAL EXAM.	DATE					1940			1940	DATE					TOTAL EXAM.
	10-10	9-9	8-20	7-30	6-18	6-4			6-4	6-18	7-30	8-20	9-9	10-10	
25	F	F	F	F+	F+	F	SHOULDER	ABDUCTORS	F	F+	F+	F	F	F	25
2	..	..	..	..	..	F+		ADDUCTORS	F+	..	..	..	..	..	2
2	..	..	..	..	..	F		FLEXORS	F	..	..	..	..	..	2
2	..	..	..	..	..	F+		EXTENSORS	F+	..	..	..	..	..	2
27	F	F	F	F	F+	F+	ELBOW	FLEXORS	F+	F+	F+	F+	F	F	27
27	F+	F	F-	F	F-	F		EXTENSORS	F	F	F	F-	F	F+	27
2	..	..	..	..	..	F+	PRONATORS		F	..	..	..	..	..	2
2	..	..	..	..	..	F+	SUPINATORS		F+	..	..	..	..	..	2
24	..	F	F	F	G-	G-	WRIST	FLEXORS	F+	G-	F+	F+	F	..	24
24	..	F	F	F+	G	F+		EXTENSORS	G	G	F+	F	F+	..	24
26	F	F	F+	F-	F	F+	HIP	FLEXORS	F+	F-	F+	F+	F	F	26
9	..	..	..	..	F	F		EXTENSORS	F	F	..	..	..	..	9
8	..	..	..	..	G	G		ABDUCTORS	G	G-	..	..	..	..	8
2	..	..	..	..	..	F-		ADDUCTORS	F-	..	..	..	..	..	2
25	F+	F	F	F+	F+	G	KNEE	FLEXORS	G-	F+	F+	F	F	F+	25
27	F	F-	F+	F+	F+	F		EXTENSORS	F-	F+	F+	F+	F-	F	27
26	N	G	G+	G	G	G+	ANKLE	FLEXORS	G+	G	G	G+	G	N	26
24	F+	F+	F+	F+	F+	G-		EXTENSORS	G-	F+	F+	F	F	F+	24
4	..	..	..	..	..	F	SPINE	EXTENSORS	F	..	..	..	..	..	4
5	..	..	..	..	F	F	ABDOMEN	RECTUS	F	F	..	..	..	..	5
3	..	..	..	..	..	F	ABDOMEN	OBLIQUE	F	..	..	..	..	..	3
Total 293															Total 293

Fig. 1.—The two lateral columns show the total number of muscle examinations made in all patients. The remainder of the chart is the record of one of the patients and is fairly typical of the entire study.

Case 3.—N. K. (History No. A-22252), a white male aged 8 years, had had onset at 4 years of age. Diagnosis was typical pseudohypertrophic muscular dystrophy, ambulatory.

(1) On June 4, 1940, he received B_6, 100 mg., intravenously, twice weekly for sixteen doses, with no improvement. (2) On July 30, 1940, he received intramuscular α-tocopherol in oil, 25 mg., seventeen injections in thirty-six days, with no improvement. (3) On Sept. 9, 1940, he was given oral TRN6 daily (as in Case 2) for thirty-five days. No improvement was noted. The child lost 1 kg. (2.2 pounds) in weight in four months.

CASE 4.—M. F. (History No. A-42454), a white male aged 5 years, had showed onset of symptoms at 4½ years of age. The diagnosis was typical pseudohypertrophic muscular dystrophy, ambulatory. (This patient and the patient in Case 5 were brothers.)

(1) On May 25, 1940, he received oral wheat germ oil, 1 c.c. daily for fifty-eight days, without improvement. (2) On July 22, 1940, he was given B_6 orally, 100 mg. daily for twenty-one days, with no improvement; (3) on Aug. 12, 1940, intravenous B_6, 50 mg. daily for twenty-eight days, with no improvement; (4) on Sept. 9, 1940, oral TRN6 (as in Case 2) daily for thirty-one days. No improvement was noted in the muscles although the child gained 1.2 kg. in ten weeks and felt better.

CASE 5.—J. F. (History No. A-42453), a white male aged 10 years, showed onset at 8 years of age (brother of patient in Case 4). Diagnosis was typical pseudohypertrophic muscular dystrophy, ambulatory.

(1) On May 25, 1940, the patient received oral wheat germ oil, 1 c.c. daily for fifty-eight days, with no improvement; (2) on July 22, 1940, oral B_6, 100 mg. daily for twenty-one days, without improvement; (3) on Aug. 12, 1940, intravenous B_6, 50 mg. daily for twenty-eight days, with no improvement; (4) on Sept. 9, 1940, oral TRN6 (as in Case 2) daily for thirty days, with no improvement.

CASE 6.—R. H. (History No. 70776), a white male aged 14 years, had developed symptoms at 7 years of age. Diagnosis was typical pseudohypertrophic muscular dystrophy. He had not walked for fifteen months because of contractures of the hamstrings. His muscle power was fair. (1) On June 10, 1940, he received oral B_6, 100 mg. daily for thirty days, with no improvement.

DISCUSSION

In two patients who received wheat germ oil by mouth for two months and in one patient who received α-tocopherol intramuscularly on alternate days for thirty-six days, we were able to determine no improvement when careful muscle tests were done.

Four patients received vitamin B_6 orally, 100 mg. daily, for periods of twenty-one to thirty-six days. Since oral administration of B_6 resulted in no improvement and since biweekly injections were ineffective in two patients, four patients were given B_6 intravenously in daily doses of 50 mg. for twenty to thirty days, but the result was the same.

It was then decided to try orally a combination of thiamin chloride, riboflavin, nicotinic acid, and vitamin B_6. This was administered to four patients for thirty days. The only improvement during the entire course of therapy was a gain in weight in one patient and an improvement in the sense of well-being in the others. We attributed the improvements to the general effect of the vitamin therapy since the patients' diets had been deficient in some of the vitamins used.

SUMMARY

When careful muscle tests were performed, no improvement was noted in six patients with progressive hypertrophic muscular dystrophy after administration of wheat germ oil, α-tocopherol, vitamin B_6 orally and

intravenously, and combinations of the vitamin B complex orally. In our small series we were unable to confirm reports of favorable results with these materials.

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THE CHEMOTHERAPY OF INFECTIOUS DIARRHEA WITH SULFATHIAZOLE

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THE treatment of infectious diarrhea in the past has proved far from satisfactory. Specific therapy has been a disappointment, and dietary care has never reached a point of standardization. Chemotherapeutic agents have added little until the present. With the advent of the sulfonamide group of drugs and their dramatic effects on various other infections, it was the hope of many that their efficiency might hold in infectious diarrheas. Some reports[1-4] on the use of sulfanilamide and sulfapyridine have appeared in the literature; they were encouraging, but not convincing. Certainly in our personal experience with a few cases in 1939 these drugs were very disappointing.

Since March, 1940, we have used sulfathiazole* in the treatment of diarrhea at the Henrietta Egleston Hospital for Children with promisingly uniform results. Ching, Ware, and Witherington[5] have also reported its successful use in seven cases of infectious diarrhea without failure.

Table I

Studies on Fecal and Urinary Excretions of Sulfonamide in Dogs—Barlow

Compound	Urine	Feces	Urine and Feces
Sulfanilamide	87.8	0.25	88.05
Sulfapyridine	57.0	18.9	75.93
Sulfathiazole	56.8	27.8	88.5

The use of this drug is not without experimental basis. Lawrence[6] has shown that in vitro sulfathiazole is the most effective member of the sulfonamide group of drugs against the colon-typhoid-dysentery group of organisms. It is followed in order of decreasing effect by sulfapyridine, sulfaphenylthiazole, and sulfanilamide. Barlow[7] in his work in the research laboratory of the Winthrop Chemical Company has shown that a large proportion of the dosage of sulfathiazole administered by mouth in dogs can be recovered in the feces and that this percentage is higher than sulfapyridine or sulfanilamide. Table I shows a summary of his results. Barlow has also found that, when the sodium salt is injected intravenously, a perceptible amount of the drug is normally excreted in the feces. This latter fact indicates that the drug is excreted

From the Henrietta Egleston Hospital for Children, Atlanta, Ga.

*The drug was furnished through the courtesy of the Department of Medical Research, Winthrop Chemical Company.

into the intestinal tract from the blood stream. Considering the physiology of fluid balance in the body, it seems reasonable to expect an increased fecal excretion in the presence of diarrhea.

For a comparative study we have chosen the 113 cases of infectious diarrhea treated in this hospital during the ten-year period of 1930-39 as controls. Of these 113 cases, forty-nine had positive stool cultures for *B. dysenteriae*. It is impossible to present each year individually, so we are using the average for the decade. The only factor showing notable variation from year to year was the mortality figure. There has been no year without a death prior to 1940.

TABLE II

COMPARATIVE STUDY OF RESULTS OBTAINED IN INFECTIOUS DIARRHEA TREATED WITH SULFATHIAZOLE IN 1940 AND CASES TREATED WITHOUT THIS DRUG DURING PRECEDING DECADE 1930-1939

YEAR	NO. OF CASES	AVERAGE DURATION IN DAYS			HOSPITAL STAY	MORTALITY
		FEVER	DIARRHEA	BLOODY STOOLS		
1940	17	1.62	2.25	1.5	5.8	0
1930 to 1939	113	11	14	8.1	21	39

Table II presents a summary of the results of chemotherapy with sulfathiazole in 1940 compared with the cases treated during the preceding decade without such chemotherapy. These figures are in the main self-explanatory, but it might be well to clarify a few points. Of the seventeen patients with infectious diarrhea, eleven received the drug immediately on admission to the hospital. In six instances the chemotherapy was delayed for two to four days in order that the diagnosis might be definitely established. In each of these cases the criteria for instituting chemotherapy was the failure of the patients to respond to the routine therapy being used. In computing the average duration of the disease and its various manifestations, we have therefore figured from the time the drug was started rather than from the day of admission to the hospital. Of the seventeen cases presented, nine were proved to be bacillary dysentery by positive stool cultures. Of these, three were Flexner, two Shiga, and four Hiss Y type organisms. Each type responded uniformly with no stool being positive on the fourth day.

Our control patients treated during the decade 1930-39 were given the routine therapy which was being used at the time of admission. The routine varied so widely that it would be impossible to enumerate details. In 1940 dehydration was first taken care of by use of parenteral fluids as indicated. In the early cases we used a twenty-four-hour starvation period followed by either skimmed milk or high carbohydrate-low bulk diet. After a few cases, however, we omitted the starvation period. In our later cases the patients were placed directly on a soft, low residue diet suitable for the age. This latter procedure did not retard improve-

ment. In no cases were bismuth, paregoric, atropine, or other medications used to aid in checking the diarrhea.

With the exception of the six cases previously mentioned, the drug was started on admission. In each instance the drug was administered orally. In most cases the daily dose was 1.5 grains per pound of body weight, and in no instance was it less than 1 grain per pound. On this dosage we obtained an average blood sulfathiazole concentration of 4.1 mg. per cent, with extremes of 1.9 mg. and 6.6 mg. The average duration of administration was 4.5 days with extremes of two and eight days. In no instance was there recurrence of diarrhea after cessation of drug therapy. There was no evident toxicity from the drug until our last case. This child developed drug fever and an erythema multiforme-like rash. The fever and rash rapidly disappeared when the drug was discontinued.

Although it is difficult to show statistically, we were very much impressed by the rapidity of improvement in the general condition of our patients. We feel that this can be attributed to the rapid response of the toxic reactions and to the fact that we were free to give these patients diets which would satisfy caloric demands much earlier. Many of these patients were in condition to be discharged earlier had we not held to our routine of having three negative stool cultures before permitting discharge.

Four typical case records are presented to illustrate the uniformity of the results obtained with sulfathiazole therapy.

CASE 1.—M. E. F., a white female, aged 2 years, was admitted on March 7, 1940. She had a history of onset on March 3 with thirty to forty bloody stools daily and high fever. Examination revealed an acutely ill, badly dehydrated infant. Temperature was 103° (R). Stools were positive for *B. dysenteriae*, Flexner type. She was given intravenous fluids continuously for 18 hours and then put on liquid, high carbohydrate diet. Fever and diarrhea continued unabated. On March 10 the patient was put on sulfathiazole without other change. After twelve hours the temperature was normal, and diarrhea subsided. The first stool culture checked after starting the drug was on March 14, and this was negative.

CASE 2.—G. P., a white female, aged 13 months, was admitted on July 28, 1940, because of numerous bloody stools and high fever. Examination showed an emaciated, dehydrated, acutely ill child. Temperature was 102° (R). Stools were positive for *B. dysenteriae*, Shiga type. She was given 250 c.c. fluid subcutaneously and put on sulfathiazole with high carbohydrate, soft diet. Fever and diarrhea subsided quickly. Stool culture was negative on August 2.

CASE 3.—B. N., a white female, aged 10 months, was admitted on June 29, 1940. She had a history of onset with high fever and innumerable stools with blood. Examination revealed an emaciated, dehydrated, acutely ill infant. Temperature was 103° (R). Stool culture was positive for Hiss Y type. She was put immediately on sulfathiazole with skimmed milk formula. Temperature was normal within twenty hours, and stools cleared rapidly. Culture of stool on July 2 was negative.

CASE 4.—J. R., a white female, aged 11 months, was admitted on September 22, 1940. Onset was on September 16 with numerous bloody stools and fever. Examina-

tion revealed a dehydrated, acutely ill child. Temperature was 103° (R). Stool cultures were negative three times. She was given intravenous fluids for dehydration and also was started immediately on sulfathiazole and infant soft diet. Temperature was normal after twenty hours, and stools improved rapidly.

We also administered sulfathiazole to sixteen patients with so-called noninfectious diarrheas. The differentiation between infectious and noninfectious diarrheas is often extremely difficult. Our criteria for the latter diagnosis were the absence of prolonged, severe toxic symptoms, the absence of pus in the stool, and the absence of an appreciable amount of blood. Of course no patients with positive stool cultures for *B. dysenteriae* were included in this group. Table III presents a summary of this group of cases compared with 111 similar cases treated without the drug during the past decade. Also shown are eleven cases which did not have the drug this year because they were mild on admission. Here again it will be noted that our results were very satisfactory. The dietary regime in this group was similar to that used in the infectious cases. The results in these cases suggest again the possibility that there may actually be an infectious basis for our so-called noninfectious diarrheas.

TABLE III

COMPARATIVE STUDY OF RESULTS OBTAINED IN NONINFECTIOUS DIARRHEA TREATED WITH SULFATHIAZOLE IN 1940 AND CASES TREATED WITHOUT THIS DRUG DURING PRECEDING DECADE 1930-1939 AND 1940

YEAR	NUMBER CASES	DURATION IN DAYS		MORTALITY
		DIARRHEA	HOSPITAL STAY	
1940 (treated)	16	2	6	0
1940 (untreated)	11	6	11	0
1930 to 1939	111	10	17.5	15

SUMMARY

Laboratory data which would suggest that sulfathiazole might be a satisfactory chemotherapeutic agent in infectious diarrhea are presented.

Clinical results obtained in seventeen cases of infectious diarrheas treated with sulfathiazole are presented. These are excellent results, when compared to 113 similar cases treated during the preceding decade without chemotherapy.

Also presented are sixteen cases of noninfectious diarrhea treated with the drug with equally good results.

COMMENT

We have presented a study of seventeen cases of infectious diarrhea and sixteen cases of noninfectious diarrhea treated with sulfathiazole. While this group is too small for the results to be considered conclusive, we do feel that we now have a chemotherapeutic agent which has given promisingly uniform results in the treatment of diarrhea.

We are indebted to Doctor M. Hines Roberts for his suggestions and criticisms and to the members of the Attending and Resident Staff of Henrietta Egleston Hospital for their cooperation in this work.

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THE VALUE OF CONVALESCENT CARE FOR RHEUMATIC CHILDREN

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IN RECENT years an ever-increasing interest has been shown in convalescent care for children suffering from rheumatic disease. A number of papers are found in the literature dealing with various phases of convalescent care for rheumatic disease. Many reasons for the value of convalescent care have been suggested.[1] Some believe that group control under the instruction of a competent staff provides the essential medical care and makes possible the adjustment of the individual child's activity to the functional capacity of his heart.[2] Others stress the importance of emotional readjustment in these children and believe that group control leads to the disappearance of most of the undesirable emotional mechanisms established in the homes of these patients.[3] The value of convalescent care for rheumatic children has been particularly stressed in England and in recent years remarkable progress has been achieved there in developing resources for the care of children in convalescent hospitals. It was estimated in 1938 that there were 1.7 beds for each 1,000 elementary school children.[4]

In this country long range studies have been made to determine whether convalescent care affects the end results of rheumatic disease.[5] Some investigators have studied mortality figures in a group of convalescent children after an interval of ten years and concluded that the life cycle is increased in this group.[6] Others have studied a group of rheumatic children after an interval of fifteen years from the period of convalescent care and arrived at the impression that the educational, hygienic, and medical facilities offered to children at a convalescent home influence favorably the life of these individuals.[7]

In view of the fact that rheumatic disease in childhood has been frequently compared with tuberculosis, it has been suggested that the care of patients with rheumatic disease should follow along lines already proved beneficial for tuberculosis. Thus far, however, no conclusive evidence has been presented to show precisely what role convalescent care plays in the course of this disease.

The purpose of this preliminary study is to evaluate the results of convalescent care given to a group of rheumatic children at St. Francis Sanatorium for Cardiac Children. For comparison, a control group was selected for study and observed at the Children's Cardiac Clinic of the Kings County Hospital during the same period of time (thirty-six months).

Five factors were studied: (1) gain in weight; (2) the occurrence of upper respiratory infection; (3) the incidence of rheumatic recur-

From St. Francis Sanatorium for Cardiac Children, Roslyn, Long Island, and Children's Cardiac Clinic of King's County Hospital.

rences; (4) the relation of upper respiratory infection to rheumatic recurrences; (5) the effect of the patient's living conditions at home upon the course of the disease after convalescent care.

TABLE I

COMPARISON OF CONVALESCENT AND CONTROL GROUPS OF CHILDREN

	CONVALESCENT GROUP* (110 CHILDREN)	CONTROL GROUP† (110 CHILDREN)
Age (years):		
Youngest	6.0	6.0
Oldest	14.0	14.0
Average	11.4	11.1
Course of Disease:		
Age at onset (years)	7.2	7.6
Duration of disease (years)	3.6	3.5
Duration since last attack (months)	12.1	11.9
One acute attack	55	60
Two acute attacks	30	28
Three or more acute attacks	25	22
Cardiac Damage:		
Mitral insufficiency	66	76
Mitral stenosis and insufficiency	40	29
Mitral and aortic disease	4	5
Home Environment:		
Good	24	28
Fair	52	49
Bad	34	33

*In this and succeeding charts, "convalescent group" refers to children at St. Francis Sanatorium for Cardiac Children.

†"Control group" refers to children attending Kings County Hospital Cardiac Clinic and living at home.

One hundred and ten rheumatic girls, 6 to 14 years of age, were under observation for thirty-six months.* The average period of observation prior to admission to the sanatorium was fourteen months. The average period of convalescent care was 8.3 months and the average period of observation after discharge was 14.5 months. A control group of 110 rheumatic children, fifty boys and sixty girls, 6 to 14 years of age, was observed at the same time.† This group was selected to match the convalescent group. Table I shows that the two groups were comparable.

*The St. Francis Sanatorium for Cardiac Children, Roslyn, Long Island, was opened in February, 1937. Admissions were limited to girls 6 to 14 years of age with a definite rheumatic history and a functional classification of I, II, E, and F (New York Heart Association Classification[5]). Complete clinical records were kept. Physical examinations and complete laboratory data were recorded at frequent intervals.

The therapeutic measures offered these children conformed to the general principles of convalescence which emphasize nutrition, relaxation, rest, and childhood contentment and happiness. No medication was given except in the course of an intervening illness when symptomatic treatment was administered. No therapeutic measures aimed at the prevention of upper respiratory infections and subsequent rheumatic recurrences were attempted. This group was not a "closed colony" during the period of observation.

†This group of cases was collected from the Children's Cardiac Clinic of the Kings County Hospital. The large clinic attendance made possible the matching of the two groups. The medical supervision was the same in both groups. The 50 boys and 60 girls were compared as to age, course of rheumatic history, degree of cardiac involvement, and home living conditions and were found entirely comparable.

GAIN IN WEIGHT

It is a common observation that loss of weight or failure to gain weight in a rheumatic child is often the only evidence of a subclinical rheumatic carditis, sometimes "occurring as a percursor, months in advance, of a fulminating acute carditis."[9] Since loss of weight is considered indicative of rheumatic activity, the marked gain of weight in the convalescent group of children is noteworthy. Of the entire group of children, only three failed to gain appreciably at the sanatorium. The rest of the group added weight quickly and in large amounts. The gain of weight was independent of season. Children who were admitted shortly after an acute episode did not fall behind or get ahead of those who had been quiescent for a longer period of time.*

TABLE II

AVERAGE WEIGHT GAINED DURING STAY AT SANATORIUM, ARRANGED ACCORDING TO AGE

AGE (YR.)	AVERAGE WEIGHT OF NORMAL CHILD* (LB.)	AVERAGE WEIGHT ON ADMISSION TO SANATORIUM (LB.)	AVERAGE GAIN PER CHILD AT SANATORIUM (LB.)	PER CENT OF BODY WEIGHT GAINED
6- 7	46.0	42.3	6.9	16.0
7- 8	50.0	51.7	8.9	17.2
8- 9	54.6	65.2	12.4	18.9
9-10	59.5	67.0	12.0	17.9
10-11	65.0	76.1	18.8	24.6
11-12	71.0	72.5	18.8	25.8
12-13	78.0	83.0	21.6	25.9

*Diseases of Infancy and Childhood, Holt and Howland, D. Appleton & Co., ed. 8, chap. II, p. 22.

The average gain in weight ranged between 16 per cent of body weight for the 6- to 7-year group and 26 per cent of body weight for the 12- to 13-year group (Table II). This is particularly noteworthy, as the weight on admission to the sanatorium did not differ in any significant degree from the average weight of normal children of the same age group. The older the child, the greater the increment of weight, and the greatest increase was found, as might be expected, among the group approaching adolescence.

In order to compare the convalescent group and control group with respect to gain in weight, it became necessary to reduce the data to the comparable unit of weight gain per month. A study of Chart 1 shows that the monthly gain in weight in the treated group was two to three times that of the control group. It is of some significance that during the convalescent period these children gained two to five times as much as during the period of observation preceding admission to the sanatorium and two to three times as much as would be expected in a normal

*All children ate well. No effort was made to increase the caloric intake of thin children or decrease it in stout children. The diet consisted of well-balanced, wholesome, appetizing food. Special attention was given to the intake of green vegetables and fruits. Each child consumed 1 quart of milk daily.

group within the same age range. The monthly gain in weight after discharge is definitely smaller than during the period preceding convalescent care.

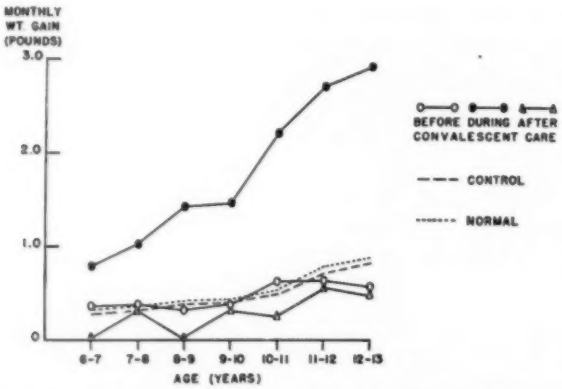

Chart 1.—Comparison of monthly gain in weight for normal children, rheumatic children (control group), and rheumatic children under convalescent care.

THE INCIDENCE OF UPPER RESPIRATORY INFECTION

Observation of 110 children at St. Francis Sanatorium shows that the incidence of infection of the respiratory tract was low as compared with that of the control group (Table III, Chart 2). The highest incidence occurred during the winter and early spring months. Nothing unusual was noted about the clinical course of the respiratory infection.* No complications were observed.†

TABLE III

NUMBER OF ATTACKS OF UPPER RESPIRATORY INFECTIONS IN THE CONVALESCENT GROUP AS COMPARED WITH THE CONTROL GROUP

	NUMBER OF PATIENTS	OBSERVATION PERIOD (AVERAGE MONTHS)	UPPER RESPIRATORY INFECTIONS	
			TOTAL ATTACKS	ATTACKS PER CHILD PER YEAR
Convalescent Group				
Before convalescent care	110	14.0	242	1.67
During convalescent care	110	8.3	36	0.47
After convalescent care	110	14.5	136	1.02
Total period of observation	110	36.8	414	1.22
Control Group	110	36.0	604	1.83

The occurrence of infection of the respiratory tract in this group after discharge from the sanatorium was also low as compared with the con-

*Of thirty-six children in this group, fifteen had acute follicular tonsillitis, with a febrile course lasting four to eight days, and with the usual complaints of sore throat, anorexia, and fatigue; the remaining twenty-one children had a milder form or rhinopharyngitis, with a febrile course of one to three days followed by complete recovery in three to five days.

†The treatment was entirely symptomatic. Gargle, forcing of fluids, and a small dose of salicylates was the treatment offered in all cases. Occasionally "nose drops" were used.

trol group (Table III, Chart 2). Here also, the type of infection was milder than that observed in the control group.

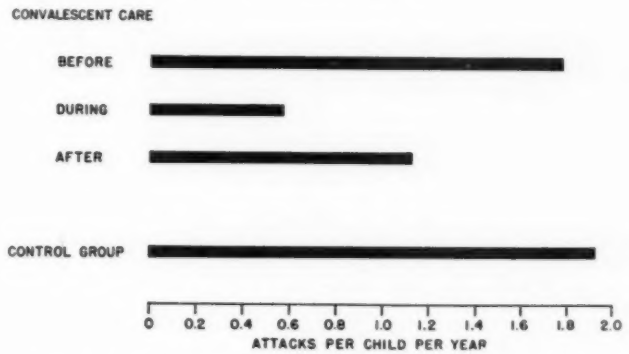

Chart 2.—Number of upper respiratory infections per child per year for convalescent and control groups of rheumatic children.

THE INCIDENCE OF RHEUMATIC RECURRENCES

It is common knowledge that rheumatic infection may exist within the body for months or years without clinical signs or symptoms of active infection. In many instances, however, without any prodromal syndrome or any evidence of reinfection, the rheumatic process suddenly flares up. This recrudescence or recurrence may take the form of any of the recognizable manifestations of rheumatic fever, i.e., acute polyarthritis, chorea, acute pancarditis, etc. It is also well known that the extent of cardiac damage is directly proportional to the number of such recurrences. It is, therefore, of some significance that the incidence of rheumatic recurrences is lower during and following convalescent care than preceding it. In the treated group, rheumatic recurrences were one-third as common as in the control group. Of 110 children, only fifteen had rheumatic recurrences during the period of convalescent care of over eight months, and thirty had acute exacerbations during the posteonvalescent period of 14.5 months. The same group of children had seventy-two rheumatic recurrences during a fourteen-month period of observation preceding convalescent care (Table IV).

TABLE IV

RHEUMATIC RECURRENCES IN THE CONVALESCENT AND CONTROL GROUPS

	NUMBER OF PATIENTS	OBSERVATION PERIOD (AVERAGE MONTHS)	RHEUMATIC RECURRENCES	
			TOTAL ATTACKS	ATTACKS PER CHILD PER YEAR
Convalescent Group				
Before convalescent care	110	14.0	72	0.56
During convalescent care	110	8.3	15	0.18
After convalescent care	110	14.5	30	0.22
Total period of observation	110	36.8	117	0.34
Control Group	110	36.0	183	0.55

During the entire period of observation of three years, these 110 children had 117 rheumatic recurrences, as compared with 183 recurrences in the control group observed during the same period of time. Prior to convalescent care, the incidence of rheumatic recurrences per child per year in the control and treated groups was the same. The incidence of rheumatic recurrences in the control group remained the same

TABLE V

TYPE AND SEVERITY OF RHEUMATIC RECURRENCES IN GROUP RECEIVING CONVALESCENT CARE AS COMPARED WITH CONTROL GROUP

	NUMBER OF CHILDREN	NUMBER OF ATTACKS				DAYS OF ACTIVE ILLNESS PER CHILD	MORTALITY (%)
		TOTAL	ARTHRITIS	CARDITIS*	CHOREA		
Convalescent Group Postsanatorium period	110	30	8	16	6	58	0
Control Group Same period	110	58	14	38	6	92	4.5

*Carditis: The term active carditis refers to involvement of the cardiac structure and is all inclusive. From post-mortem examinations, it becomes evident that usually when the heart is involved in rheumatic disease, the involvement is widespread and affects, in varying degree, the pericardium, the endocardium, and the myocardium. Thus, active carditis includes acute pericarditis, endocarditis, and myocarditis.

For an excellent summary of the symptomatology and physical signs of rheumatic carditis, the reader is referred to Wilson's book, "Rheumatic Fever," p. 159, Table 36.*

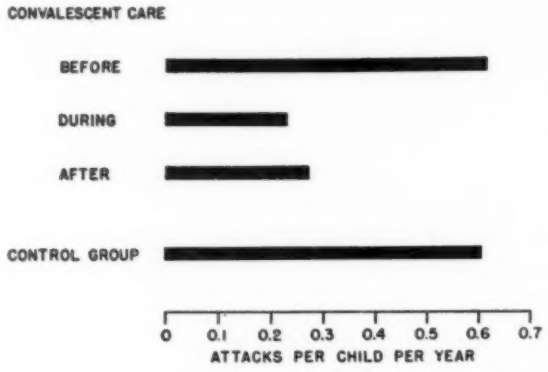

Chart 3.—Number of rheumatic recurrences per child per year for convalescent and control groups of rheumatic children.

throughout the period of observation, while the incidence of rheumatic recurrences in the treated group fell to one-third of this value during the following convalescent care (Chart 3). Furthermore, after convalescent care the active episodes were milder and of shorter duration than in the control group.* (Table V.)

*All the active episodes in the convalescent and control groups were treated in the same institution and by the same personnel.

THE RELATION OF UPPER RESPIRATORY INFECTION TO RHEUMATIC RECURRENCES

The association of upper respiratory infection and recurrent attacks of rheumatic fever has been discussed for many years. In recent years this relationship has become a controversial issue. There are those who claim that there is a close relationship between streptococcal respiratory infections and the onset of a primary or recurrent attack of rheumatic fever.[10] Others find that 67 per cent of rheumatic recurrences are clinically associated with infections of the respiratory tract.[11] Still others claim that upper respiratory infection bears no specific etiological relationship to rheumatic disease; the frequent association is considered due to chance.[12]

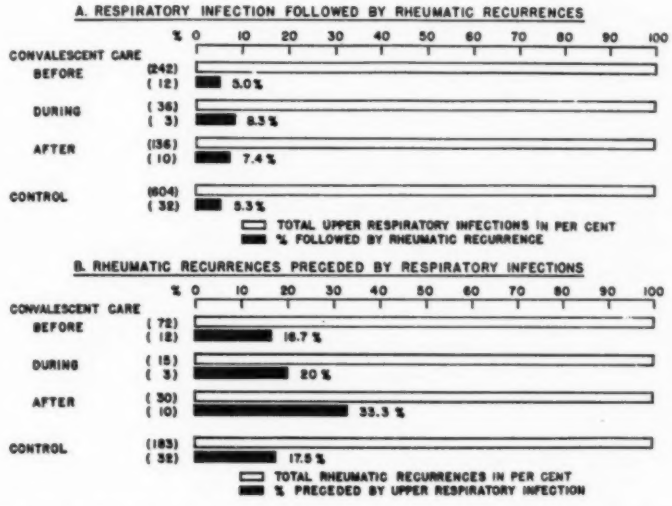
A. RESPIRATORY INFECTION FOLLOWED BY RHEUMATIC RECURRENCES
% 0 10 20 30 40 50 60 70 80 90 100
CONVALESCENT CARE
BEFORE (242) (12) 5.0%
DURING (36) (3) 8.3%
AFTER (136) (10) 7.4%
CONTROL (604) (32) 5.3%
TOTAL UPPER RESPIRATORY INFECTIONS IN PER CENT
% FOLLOWED BY RHEUMATIC RECURRENCE
B. RHEUMATIC RECURRENCES PRECEDED BY RESPIRATORY INFECTIONS
% 0 10 20 30 40 50 60 70 80 90 100
CONVALESCENT CARE
BEFORE (72) (12) 16.7%
DURING (15) (3) 20%
AFTER (30) (10) 33.3%
CONTROL (183) (32) 17.5%
TOTAL RHEUMATIC RECURRENCES IN PER CENT
% PRECEDED BY UPPER RESPIRATORY INFECTION

Chart 4.—Relation of upper respiratory infection to rheumatic recurrences.

The seasonal flux of infection of the respiratory tract was concurrent with the flux of rheumatic recurrences. No sequential relationship between the two was observed. During the period of convalescent care only three children of the thirty-six with upper respiratory infection had rheumatic recurrences apparently following these infections. On the other hand, of the fifteen children who had recurrences, in only three cases was the active episode preceded by an upper respiratory infection. Similarly, this group of children presented no sequential relationship between upper respiratory infection and reactivation of the rheumatic process after discharge from the sanatorium during an average follow-up period of 14.5 months.

In the control group of children, followed for the entire period of thirty-six months, 604 attacks of upper respiratory infection were ob-

TABLE VI

RELATION OF UPPER RESPIRATORY INFECTIONS TO RHEUMATIC RECURRENCES IN CONVALESCENT AND CONTROL GROUPS

	NUMBER OF PATIENTS	OBSERVATION PERIOD (AVERAGE MONTHS)	UPPER RESPIRATORY INFECTION			RHEUMATIC RECURRENCES		
			WITH RHEUMATIC RECURRENCES	WITHOUT RHEUMATIC RECURRENCES	PERCENTAGE WITH RHEUMATIC RECURRENCES	WITH U.R.I.*	WITHOUT U.R.I.	PERCENTAGE WITH U.R.I.
Convalescent Group								
Before convalescent care	110	14.0	12	230	5.0	12	60	16.7
During convalescent care	110	8.3	3	33	8.3	3	12	20.0
After convalescent care	110	14.5	10	126	7.4	10	20	33.3
Total period of observation	110	36.8	25	389	6.4	25	92	21.3
Control Group	110	36.0	32	572	5.3	32	151	17.5

*Upper respiratory infection.

served. Of these, only thirty-two seemed to have been followed by rheumatic recurrences, 572 attacks of upper respiratory infection not showing any such sequence. On the other hand, during the same period, 183 rheumatic recurrences were observed, of which only thirty-two seemed to have been preceded by upper respiratory infection, 151 showing no such sequence (Table VI, Chart 4).

Furthermore, no relationship between the severity of the upper respiratory infection and rheumatic recurrences was noted. The three cases of rheumatic recurrences apparently were associated with upper respiratory infection following mild rhinopharyngitis, while fifteen cases of acute follicular tonsillitis were not followed by rheumatic recurrences (Table VII).

TABLE VII

TYPE OF UPPER RESPIRATORY INFECTION AND ITS RELATION TO RHEUMATIC RECURRENCES IN CONVALESCENT GROUP

UPPER RESPIRATORY INFECTION	TOTAL ATTACKS	ACUTE FOLLICULAR TONSILLITIS	MILD RHINITIS AND PHARYNGITIS
Followed by rheumatic recurrence	3	0	3
Not followed by rheumatic recurrence	33	15	18
Total	36	15	21

THE EFFECT OF ENVIRONMENTAL LIVING CONDITIONS AFTER CONVALESCENT CARE UPON THE COURSE OF RHEUMATIC DISEASE

Many factors may vitiate the improvement made during convalescent care. It is reasonable to assume that the longer the period of time elapsing after discharge from the sanatorium, the greater the possible chance for a recrudescence. The season of the year in which the child returns to his home environment may play a significant role in the incidence of recurrences. The patient's living conditions after discharge from the sanatorium may predispose him to a reactivation of the rheumatic infection. Exposure to rheumatic infection in the family is sometimes considered a cause of exacerbation of the rheumatic process.

A detailed study was made of the home environment of the 110 children in the sanatorium. Many factors in their living conditions were considered. The details of this study form the subject of another communication. In general, living conditions were considered "good" where there was an adequate budget, a well-balanced diet, ample clothing in the winter, sensible maternal care, and dry and sunny sleeping quarters. Where two of the above factors were lacking, the home environment was considered "fair." A home in which three or more factors were lacking was considered "poor."

During the period of 14.5 months following convalescent care, thirty of 110 children had rheumatic recurrences and eighty remained free of active episodes. A comparison of these two groups of children was

undertaken. It was observed that the two groups were parallel as to age distribution (Chart 5). The age of onset of rheumatic disease in the group who had recurrences was 7.8 years as compared with 7.0 years for the group without recurrences. The duration of the disease in the first group was 3.6 years as compared with 3.8 years for the second group.

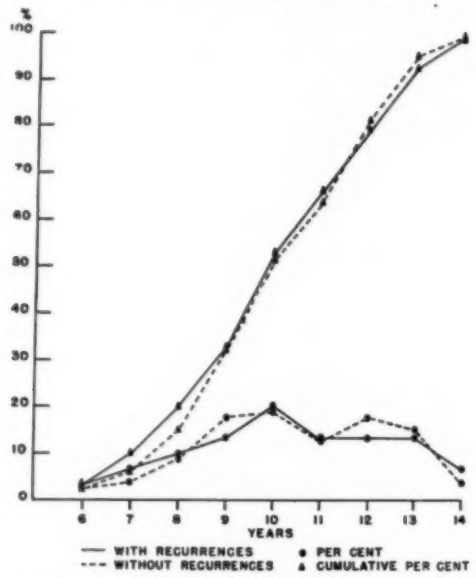

Chart 5.—Age distribution of thirty cases with recurrences and eighty without recurrences after convalescent care.

TABLE VIII

DURATION OF STAY AT SANATORIUM AND PERIOD OF FOLLOW-UP AFTER DISCHARGE FROM SANATORIUM

	DURATION OF STAY AT SANATORIUM (AVERAGE MONTHS)			POSTCONVALESCENT OBSERVATION PERIOD (AVERAGE MONTHS)		
	TOTAL	WINTER	SUMMER	TOTAL	WINTER	SUMMER
For all cases	8.3	3.9	4.4	14.5	7.2	7.3
Cases with recurrences	8.6	4.0	4.6	15.1	8.4	6.7
Cases without recurrences	8.4	4.0	4.4	14.7	7.1	7.6

The length of the quiescent period preceding admission to the sanatorium was 11.8 months for the first group as compared with 12.2 months for the second group. Both groups of children remained at the sanatorium for a similar period of about eight months and were observed after discharge for approximately 14.5 months (Table VIII). In respect to the presence of rheumatic infection in the family, type of rheumatic history, degree of cardiac damage, progress at the sanatorium and progress since discharge, the two groups were comparable (Table IX).

TABLE IX

COMPARISON OF GROUP OF CHILDREN WHO SUFFERED RHEUMATIC RECURRENCES AFTER CONVALESCENT CARE WITH THE GROUP WHO REMAINED FREE OF RHEUMATIC RECURRENCES

	TOTAL CASES		WITH RECURRENCES		WITHOUT RECURRENCES		RATIO OF CASES WITH RECURRENCES TO CASES WITHOUT RECURRENCES
	NO.	%	NO.	%	NO.	%	
NUMBER OF CASES	110		30		80		1:2.6
Diagnosis							
Mitral insufficiency	66	60.0	20	66.7	46	57.5	1:2.3
Mitral stenosis and insufficiency	40	35.4	7	23.4	33	41.3	1:5.9
Mitral and aortic disease	4	3.6	2	6.7	2	2.5	1:1.0
Course Before Admission							
One acute attack	55	50.0	14	46.7	41	51.2	1:2.9
Two acute attacks	30	27.3	9	30.0	21	26.3	1:2.3
Three or more acute attacks	25	22.8	7	23.4	18	22.5	1:2.6
Rheumatic infection in family	31	28.1	9	30.0	22	27.5	1:2.4
Course at Sanatorium							
Average weight gain (lb.)	(13.9)		(13.2)		(14.4)		
Number who gained weight	107	97.5	28	93.5	74	92.5	1:2.6
Upper respiratory infection	36	32.8	10	33.3	26	32.5	1:2.6
Rheumatic recurrences	15	13.6	4	13.4	11	13.8	1:2.8
Course Since Discharge							
Average weight gain (lb.)	(7.1)		(8.7)		(6.9)		
Number who gained weight	90	81.9	25	83.5	65	81.4	1:2.6
Upper respiratory infection	110	100.0	30	27.2	80	72.8	1:2.6
Rheumatic recurrences	30	27.3	30	100.0			
Home Environment							
Good	24	21.8	3	10.0	21	26.3	1:7.0
Fair	52	42.3	11	36.7	41	51.4	1:3.7
Poor	34	31.0	16	42.5	18	22.5	1:1.1

TABLE X

RELATION OF HOME ENVIRONMENT TO THE INCIDENCE OF RHEUMATIC RECURRENCES

	GOOD	FAIR	POOR	TOTAL
A. Cases without recurrences	21	41	18	80
B. Cases with recurrences	3	11	16	30
Ratio A:B	1:7	1:4	1:1	3:8
Total cases	24	52	34	110

The only significant difference was the home environment. Of the entire group of children, twenty-four had a "good" home environment. Only one-eighth of this group had rheumatic recurrences. Fifty-two children had "fair" living conditions at home; one-fifth of this group had active episodes. Of the thirty-four children who were replaced into a "poor" home environment, slightly less than one-half had recurrences. The incidence of rheumatic recurrences during the period of observation following convalescent care was four times as high in the "poor" home environment as in the "good" one (Table X).

COMMENT

The treatment of rheumatic infection in childhood will continue to be empirical until more is known about the etiology of this disease. The present therapeutic measures attempt to prevent cardiac damage. It is generally agreed that the prevention of rheumatic recurrences is the best means of combating progressive cardiac disability. If it can be shown that prolonged convalescent care will prevent recurrences, the morbidity and mortality figures for rheumatic heart disease will be materially diminished.

We realize that our presentation is based on a small number of cases and a short period of observation. Our results, however, are suggestive enough to indicate that prolonged convalescent care favorably influences the course of the disease. In our group of patients receiving convalescent care, the incidence of rheumatic recurrences was definitely lowered. Furthermore, rheumatic activity was found to be apparently of a milder type after convalescent care than in a control group of rheumatic children.

That home environment seems to play a significant role in the natural history of rheumatic disease has been discussed for many years.[13] Our observations point to the fact that the reactivation of the rheumatic process finds a more fertile field in a poor home environment than in a good one. It is significant that children who come to the sanatorium from a poor home environment are as free from rheumatic recurrences while at the sanatorium as those who come from a good home environment. Furthermore, it was shown that children who return to a good home environment after convalescent care have significantly fewer recurrences than those who return to poor living conditions.

These observations seem to indicate that convalescent care favorably influenced the course of the disease in the majority of children under observation. In addition, it is apparent that if children return to a poor home environment, much of the benefit derived from convalescent care is lost. Every effort should be made to improve the home environment before the children are discharged from convalescent care.

SUMMARY

One hundred and ten rheumatic children, 6 to 14 years of age, were observed at the St. Francis Sanatorium for Cardiac Children. This group was compared with a control group of 110 children from the Kings County Children's Cardiac Clinic. The period of observation was the same in both groups (thirty-six months).

The treated group gained three times as much weight as the control group in the same period of time.

The incidence of upper respiratory infection in the treated group was one-quarter that of the control group for the same period of time.

The occurrence of rheumatic recurrences was infrequent at the sanatorium and one-half as common in the treated group after convalescent care as in the control group.

No sequential relationship between upper respiratory infections and rheumatic recurrences was observed.

The incidence of rheumatic recurrences after convalescent treatment is four times as high in children who return to a "poor" home environment as in those who have "good" living conditions at home.

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ACETARSONE (STOVARSOL) IN THE TREATMENT OF SYPHILIS IN INFANTS AND CHILDREN

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ACETARSONE or stovarsol has been used in the treatment of syphilis by mouth in France since about 1920, in Germany a few years later, and in the United States since about 1930. In the early years of its use there was much confusion about the dosage. For example, Tuscherer[1] used the same amount of the drug for a newborn infant as he did for an older child, and the doses were very large.

After using these large doses, Maxwell and Glaser[2] published a report on twenty-one cases. Two of the babies in this series had severe reactions; one died with flaccid paralysis after thirty-four days of treatment. Five older children had reactions which were not so severe. In the fatal case the child received three times as much of the drug as would ordinarily be given now, and the second infant with severe reaction received four times as much as would now be used over the same period.

Martin, quoted by Maxwell and Glaser, used even larger doses, more than twice as much as Maxwell and Glaser. He reports two infants; one, aged 3 months, developed flaccid paralysis of the legs; the other, aged 2½ months, developed spastic paralysis. The dosage given was six to eight times the dose used at present.

Toxicity is an important consideration since writers of a few years ago thought acetarsone was a dangerous drug. The dosage then used was much too large, and the same routine amount was prescribed for persons of all ages. Nothing better was advanced, however, until Bratusch-Marrain[3] in 1930 advocated a dose based upon weight and directed a small beginning dose of the drug, systematically increasing the amount until the full dose was given.

This system, or a slight modification of it, has been quite generally adopted by those who use acetarsone. It advocates a dosage which is adequate but not toxic except in the case of persons who have an idiosynerasy to it.

We would like, however, to stress two exceptions to this procedure. The first is in the beginning treatment of weak, young, or premature infants with active syphilis. In those patients we think one should start with one-half the usual beginning dose for one or two weeks, or mercury or bismuth should be given for a few weeks before beginning

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the usual initial dosage of acetarsone. Instead of giving 0.005 Gm. of acetarsone per kilogram daily in this type of patient, we have given 0.0025 Gm. per kilogram daily for one week. The second week we have given the usual beginning dose of 0.005 Gm. per kilogram daily; the third week, 0.010 Gm. per kilogram daily for seven days; the fourth week, 0.015 Gm. per kilogram daily for seven days; the fifth week, 0.020 Gm. per kilogram daily is given and continued for six weeks.

As a short cut in computing dosage 0.02 Gm. per kilogram is found by writing the child's weight in pounds and pointing off two decimal places. This is correct since the number of kilograms is approximately determined by dividing the number of pounds by 2; this figure is then multiplied by 0.02; hence, pointing off two places gives the maximum dose, e.g., for a child of 60 pounds, $\frac{60}{2} \times 0.02 = 0.60$. It is then easy to compute the beginning doses. The first dose is one-fourth of this amount, save in the exception mentioned when 0.0025 per kilogram would be one-eighth of this amount.

The second exception is in the case of syphilis of the central nervous system. The usual maximum dose of 0.020 Gm. per kilogram should be further increased by one-third. We have always been able to do this with impunity when the lesser doses were well borne.

TABLE I

DOSAGE (GRAMS)	PERIOD (DAYS)
0.005 × kilograms of body weight	7
0.010 × kilograms of body weight	7
0.015 × kilograms of body weight	7
0.020 × kilograms of body weight	42

Exceptions.—1. In the case of very active syphilis or in weak babies begin with 0.0025 × kilogram body weight daily for seven to fourteen days. 2. In the case of syphilis of the central nervous system give 0.020 Gm. per kilogram daily for only one week after working up to this amount; increase to 0.025 to 0.030 Gm. per kilogram daily and continue for forty-two days.

No Rest Periods.—Alternate the above treatment with a course of bismuth or mercury.

Short Cut in Computing Dose.—A short cut in determining the usual maximum dose of acetarsone, i.e., 0.020 Gm. per kilogram: $\frac{\text{Weight in pounds}}{2} \times 0.02 = \text{usual maximum dose in Gm.}$

After completion of the above course, it is advisable to give four weeks of bismuth treatment or mercury with chalk in infants, or ten weeks with heavy metal in older children. These alternating courses should be continued until after at least one year of treatment is carried out with no signs of active syphilis and completely negative serologic tests on the blood and spinal fluid. The patient should continue to return for later check on physical findings and serologic tests at inter-

vals of six months. In no case have we had a recurrence of a positive after all tests were negative for one year.

During the ten years of our use of acetarsone 395 patients received the drug. Many of these patients moved from our locality, were transferred to private physicians or other clinics, or were otherwise lost. Even if they were treated only a short time, we felt that our records of all patients treated were valuable as a check on the toxicity of the drug.

TOXIC REACTIONS

Although most of the patients did well with the dosage which we used in the first months of our work, we think that on starting treatment it is safer to give small doses as detailed previously. With the dose like that of Tuscherer, Von Kiss, and others we had some results which in 1930 we considered due to syphilis and the complications of debility. Since that time, by using 0.005 Gm. per kilogram and in the exceptional cases 0.0025 Gm. per kilogram body weight for a period of one to two weeks, we have had some very sick infants do well.

We always impress on the child's mother or caretaker that we are using a potent drug and that it should be discontinued if fever, vomiting, loose stools, rash, or jaundice develops and that she should report the symptoms for advice.

Four of our patients died. One was a 5-month-old boy who contracted pertussis and died at home in the fifth week of bronchopneumonia. The following are abstracts of the three fatal cases treated during the early months of 1930 when the larger doses were given.

CASE 1.—A white boy, aged 4 months, weighing 12 pounds, came to the hospital with fever, bilateral discharging otitis media, large spleen and liver, and bone syphilis. He was given 0.06 Gm. of acetarsone daily for three days. He died with bronchopneumonia after three days of treatment. If 0.0025 Gm. per kilogram of body weight were given daily, this patient would have received one-fourth of this amount if treated today.

CASE 2.—A white boy, aged 3 months, weighing 10 pounds, had visceral and mucous membrane syphilis, fever, and a few fine scattered râles heard over the lung fields. He was given 0.06 Gm. of acetarsone daily for three days. This was discontinued as the child seemed very ill. He died three days after treatment was discontinued.

CASE 3.—A white girl, aged 6 weeks, weighing little less than 7 pounds, had a bloody discharge dripping from her nose and low-grade fever. Her head was retracted. There was scaling and infiltration of the region between the eyebrows, a maculopapular rash, cylindrical shaped chest and abdomen, and retraction of the lower chest with each inspiration. The liver and spleen were on a level with the umbilicus. The patient died after 0.06 Gm. of acetarsone had been given over a period of two days. This was a case of severe syphilis probably with sepsis and would have done badly in any event. However, it is likely that this large dose of arsenical hastened her death, and it is especially in such cases as these that cautious small doses are indicated.

Other reactions occurred in the first forty-one cases which were given the early type of dosage.

A white boy, aged 6 months, was given 0.06 Gm. of acetarsone for two days. He developed a temperature of 104° F. and had a convulsion which was treated by a neighborhood physician who cared for him at that time and continued his subsequent treatment for syphilis.

A white girl, aged 9 months, developed a temperature of 104° F. on the day after treatment with 0.06 Gm. of acetarsone. The drug was discontinued, and the temperature returned to normal the next day. Unmindful of the directions of the social worker, the mother again administered acetarsone (0.06 Gm.), and the temperature rose to 103° F. Gray powder was then given for two weeks, after which, acetarsone was again instituted, this time without reaction.

Since this early period we have seen reactions to acetarsone, but these have occurred only in patients apparently with an idiosyncrasy to the drug. It seems to have an excellent tonic effect on many, especially infants. There have been frequent unsolicited reports that the child almost at once began to sleep better and take food in increased amounts.

Reactions due to idiosyncrasy to the drug are also worthy of report. Skin reactions were noted several times.

A boy, aged 3½ years, developed a generalized macular rash twelve days after beginning treatment. Acetarsone was discontinued for two weeks and then resumed, the second time without reaction. A girl, aged 6 years, developed an erythema on the dorsal surfaces of the upper and lower extremities a few days after treatment was begun. No treatment was given for a week. The rash disappeared, and treatment with acetarsone was begun again, this time without reaction.

Similar erythematous reactions were seen in three other children who after a few days of treatment were again given acetarsone in smaller doses which were increased to the regular dose without reaction.

A white girl, aged 7 years, with interstitial keratitis after three weeks of treatment developed an erythema over the upper chest and dorsal surfaces of the upper and lower extremities with fever of 102° F. Acetarsone was discontinued and begun in ten days when a similar cutaneous and febrile reaction occurred. Acetarsone was not administered again. During this time, however, the keratitis made very rapid improvement; the right eye almost cleared, and the left cornea remained only slightly hazy.

One severe exfoliative reaction occurred in a girl, aged 6 years, after the full dose of acetarsone was attained. The mother noticed that an eruption was present but persisted in continuing the drug three days afterward. In this case, too, we believe that, if the drug had been discontinued on the first observation of reaction, the generalized exfoliation would not have occurred.

The rash was first noticed on the legs and arms; it was blotchy and itched intensely. When she was admitted to the hospital three days later, the rash covered the entire body and face, and the swelling and vesiculation were present over arms and legs. There were no constitutional symptoms on admission. In the following days there was extensive desquamation in the large areas, especially over the hands. The blood pressure was around 114/68. Urinary output was adequate at all times, and albumin was absent, except for a trace on one occasion. In the Mosenthal test the specific gravity varied between 1.014 and 1.026. No urobilinogen was present in the urine.

The patient was treated in a light tent. She made good progress and was discharged after a hospital period of eighteen days. The lack of serious liver or kidney damage with the extensive severe skin involvement is remarkable, and we think this speaks for the lesser toxicity of the drug.

Two additional cases of erythema, one with fever of 102° F., occurred. After the administration of the drug was discontinued and started again, beginning with a small dose, no further reaction occurred.

One 7-year-old white girl had an erythema when the very small beginning dose was given. We waited two weeks and gave one-eighth of this very small dose again. An erythema resulted. We knew then that we were dealing with an idiosynerasy to the drug and discontinued its use. She was then treated with bismuth and mercurial drugs.

One white boy, aged 9 years, was said to have a headache whenever he took mercury or acetarsone. He later took the acetarsone without trouble.

The most serious reaction that occurred after the early days of large doses was in a white girl, aged 8 years. She had been treated over a period of three years. During this period the patient had had pneumonia, frequent throat infections with high temperature, measles, and bronchopneumonia of five weeks' duration. She died with a blood and clinical picture of aplastic anemia. Her red count and hemoglobin had always been low, and she was almost continually treated for this anemia. The aplastic condition developed very suddenly.

REVERSAL OF SEROLOGY

Anyone who has had experience in the treatment of prenatal syphilis knows the frequent difficulty in getting a reversal of the serologic tests in children more than a few months old.

Reversal of serologic tests in our cases was very satisfactory. We used the Wassermann and Kahn tests until 1938 when the Eagle test was also done. Reversal was not considered complete until all tests were negative. Table II gives more details regarding reversals.

TABLE II

REVERSAL FOLLOWING	NO.	AGE ON BEGINNING TREATMENT
1st course	52	27 were 2 months or less; 8 were between 2 and 12 months; 17 were more than one year
2nd course	56	11 were 2 months or less; 25 were between 2 and 12 months; 20 were more than one year
1 year of treatment	65	6 were 2 months or less; 10 were between 2 and 12 months; 27 were more than one year
3 or more years of treatment	31	0 were 2 months or less; 2 were between 2 and 12 months; 29 were more than one year

One positive spinal fluid was found in a patient of 11 years with paresis. (In most cases spinal fluid examination was not made until the patient was under treatment for a long period.)

Reversal is not known in 115 because of transfer to other cities, clinics, or otherwise lost.

Twenty-four patients were treated but were never positive in our clinic; 22 were transferred as negative from other clinics; 1 had keratitis, screwdriver teeth, and positive F & M but was never positive; 1 had chancre of lip and was always seronegative.

Twenty-four patients are still positive and under treatment.

Signs of active syphilis disappeared very promptly after treatment with acetarsone which compared favorably with other arsenicals.

COMMENT

The advantages of treating largely or entirely by mouth are apparent, especially in children, if the results are good and the drug is safe. Our experience seems to indicate that acetarsone is both safe and efficient.

SUMMARY

Experience is given in the treatment of 395 syphilitic children using acetarsone over a period of ten years.

A résumé of complications encountered is presented.

Reversals resulted in 232 patients; twenty-two were transferred from other clinics already serologically negative; two were never positive.

Acetarsone has a definite tonic effect.

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ASCORBIC ACID ABSORPTION IN INFANTILE DIARRHEA

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THIS report deals with a study of the absorption of vitamin C when administered orally to infants suffering with diarrhea.

In a recent preliminary communication[1] it was demonstrated that ascorbic acid is excreted in small amounts in the stool of the normal infant. Adequate studies of the absorption of ascorbic acid in the intestinal tract were made possible following the development by Chinn and Farmer[2] of a method for the determination of ascorbic acid in the feces. Prior to the development of this method, numerous authors[3] had suggested that absorption of vitamin C in the intestinal tract might be interfered with in certain gastrointestinal diseases.

Low plasma blood values for vitamin C were reported by Alt, Chinn, and Farmer[4] in patients suffering with achlorhydria. Kendall and Chinn[5] pointed out that ascorbic acid is destroyed by certain bacteria isolated from human gastric contents and from guinea pig feces.

In a recent review Farmer[6] has shown, in the fasting guinea pig and rat, "that the absorption of vitamin C (l-ascorbic acid) from the intestinal tract can be explained on the basis of a simple diffusion mechanism, in which the rate of absorption varies directly with the concentration of vitamin C administered." Farmer, Abt, and Chinn[7] have reported on the absorption and excretion of vitamin C in several adults suffering with ulcerative colitis and have noticed an increased fecal loss of vitamin C in this condition when it was associated with an increased number of daily stools.

Meyer and Robinson[8] in a report from Palestine studied blood plasma values and urinary excretion in forty-three infants suffering with diarrhea, in twenty-seven of whom a diagnosis of specific bacillary dysentery had been made. They noted that the blood plasma values remained low and the urinary excretion was diminished even when these infants, during their acute diarrheal attack, were given large daily oral doses of vitamin C. When the infants recovered from their diarrhea, blood plasma values and urinary excretion returned to normal. In contradistinction to their observations on the oral administration of ascorbic acid, they noted that the parenteral administration of ascorbic acid was followed by a rise in blood plasma values and urinary excretion.

Chu and Sung[9] have reported blood plasma studies on seventeen Chinese infants and children suffering with bacillary dysentery. They noted that during the acute diarrhea the vitamin C content of the blood plasma remained low, notwithstanding the oral administration

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of fair amounts of orange juice and tomato juice. They also noted a rise in the plasma values following administration of ascorbic acid intramuscularly and intravenously, and they believed that the parenteral administration of vitamin C is indicated in children suffering with acute bacillary dysentery.

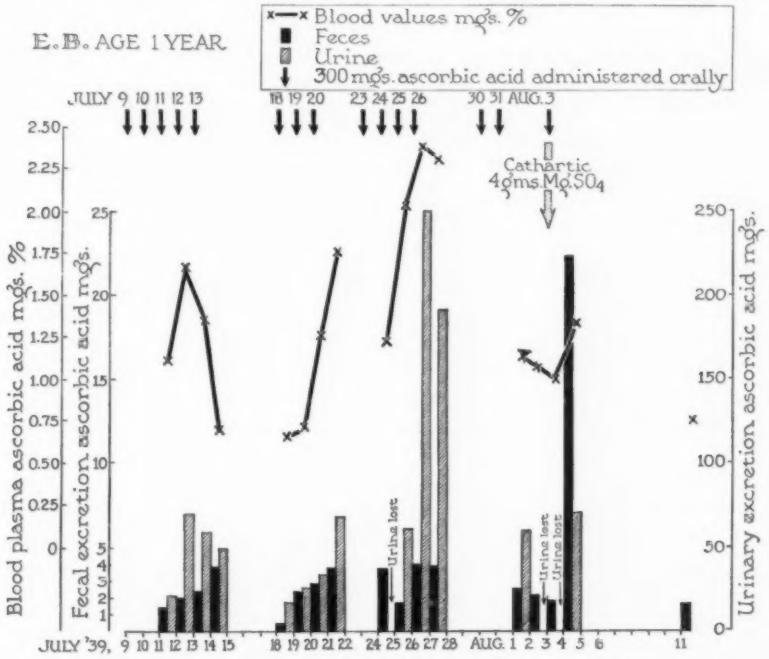
E. B. AGE 1 YEAR
Blood values mgs. %
Feces
Urine
300 mgs. ascorbic acid administered orally
Cathartic 4 gms. MgSO4
Urine lost
Blood plasma ascorbic acid mgs. %
Fecal excretion ascorbic acid mgs.
Urinary excretion ascorbic acid mgs.
JULY 9 10 11 12 13 18 19 20 23 24 25 26 30 31 AUG. 3
JULY '39, 9 10 11 12 13 14 15 18 19 20 21 22 24 25 26 27 28 AUG. 1 2 3 4 5 6 11

Fig. 1.—Normal infant, showing fecal loss of ascorbic acid during catharsis. E. B., aged 1 year, normal control, had one to two formed stools daily. The infant received an oral dose of 4 Gm. of $MgSO_4$ on August 3, 1939. Large semi-liquid stools on August 4 weighed 107 Gm. Previous average daily stool weight was 20 Gm. Twenty-four-hour ascorbic acid stool excretion on August 3 was 1.98 mg. Following catharsis, the amount recovered in stool on August 4 was 22.3 mg.

Mindlin[10] stated that in celiac disease plasma levels have failed to rise after the oral ingestion of large amounts of ascorbic acid.

As noted in the preliminary report of this investigation,[1] the fecal excretion of ascorbic acid in the normal infant is quite low, not exceeding 4 mg. daily even when large oral doses of vitamin C are administered (Fig. 1). During this experiment with the infant on the metabolism frame for four- to five-day periods, it was noted that large oral doses of vitamin C (300 mg. daily to a 1-year-old infant weighing 21 pounds), produced high blood plasma levels and greatly increased urinary excretion, with no increase in fecal excretion. The day following catharsis, when the stools were of a diarrheal nature, the fecal excretion of ascorbic acid was increased tenfold. Fecal excretion returned to normal when the stools again became solid. From this experi-

ment it may be concluded that the absorption of orally ingested vitamin C from the intestinal tract of the normal infant is practically complete. Increased motility, as produced by catharsis, interferes with normal absorption, and considerable amounts of the ingested vitamin C may be recovered in the stool.

REPORTS ON INFANTS SUFFERING WITH DIARRHEA

After establishing the level for the average daily fecal excretion of ascorbic acid in a normal infant as being quite low, below 4 mg. daily even following large amounts of orally ingested vitamin C, and after having shown that catharsis, with the production of liquid stools, will cause marked increase in fecal excretion, we began a study of the fecal excretion of ascorbic acid in infants suffering with diarrhea.

Methods Employed.—The infants were placed upon a metabolism bed, and the urine and feces were collected separately. The feces were collected in fiber containers to obviate possible oxidation of ascorbic acid by traces of metal, such as iron and copper. The blood plasma ascorbic acid levels were determined by the micromethod of Farmer and Abt.[11] The blood was drawn on a fasting stomach just prior to the administration of the vitamin supplement.* The determinations of ascorbic acid in the feces were made according to the method of Chinn and Farmer,[2] using the ascorbic acid oxidase obtained from cauliflower to differentiate the nonascorbic acid reducing substances from ascorbic acid in the stool. The twenty-four-hour urine samples were collected in dark bottles containing 10 Gm. of metaphosphoric acid, refrigerated, and titrated with a standardized Tillman's dye solution. Three infants from 2 to 3 months of age were studied. They were suffering from a nonspecific type of diarrhea, and in all three the stool cultures for the typhoid-dysentery group were negative.

CASE 1.—E. H., 2 months old, was admitted to the hospital suffering with a mild diarrhea. His stools were liquid or semi-liquid on August 15, 16, 17, and 18. The infant was placed on a protein milk formula; water and tea were administered liberally; and 200 mg. vitamin C were given orally on August 16, 17, and 18. The amount of ascorbic acid in the twenty-four-hour feces was below 1 mg. on August 15 and 16, but following the administration of 200 mg. of vitamin C by mouth the fecal excretion rose to 5 mg. on August 17 and 13 mg. on August 18, dropping to 1 mg. on August 19, when the stools had become formed (Fig. 2). The blood plasma level remained around 0.5 mg. per cent, and the urinary excretion was low.

CASE 2.—M. S., aged 2½ months, was admitted to the hospital suffering with a moderately severe diarrhea, three to four liquid stools daily, and with dehydration as manifested by diminished elasticity of the skin. The infant was placed on a protein milk formula, and tea and water were given between feedings. The stools were numerous and liquid on September 8, 9, 10, and 11 and semiliquid on September 12. The fecal excretion of ascorbic acid on September 8 and 9 was below 2 mg. Following the administration of 200 mg. of ascorbic acid orally, the

*We are indebted to Merck & Co. for supplying the ascorbic acid (Cebione) used in this investigation.

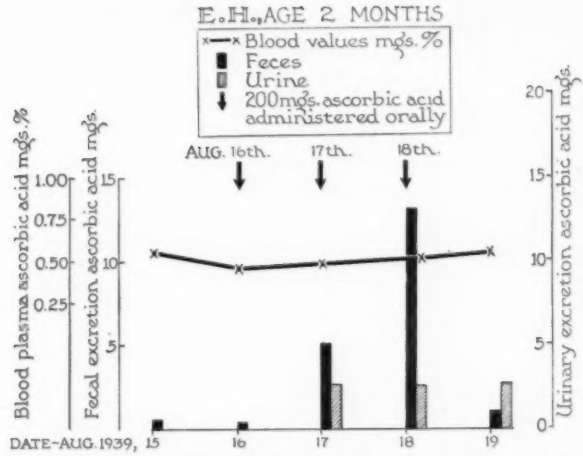

Fig. 2.—Fecal loss of ascorbic acid during diarrhea. E. H., aged 2 months, had nonspecific diarrhea, liquid stools on August 15, 16, 17, and 18, 1939, and two formed stools on August 19. The patient received 200 mg. of ascorbic acid orally on August 16, 17, and 18. There was increased fecal excretion of ascorbic acid on August 17 and 18. On August 19 the infant had two formed stools, and a corresponding marked decrease of fecal excretion of ascorbic acid was noted.

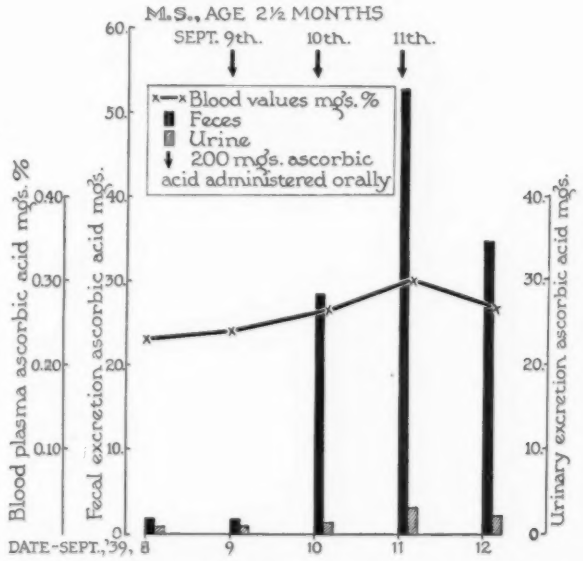

Fig. 3.—Fecal loss of ascorbic acid during diarrhea. M. S., aged 2½ months, had severe nonspecific diarrhea and dehydration, liquid stools on Sept. 8, 9, 10, and 11, 1939, and semiformed stools on September 12. The infant received 200 mg. ascorbic acid orally on September 9, 10, and 11. There was tremendous excretion of ascorbic acid in stools following large oral doses of ascorbic acid. Blood plasma ascorbic acid value was low (0.23 to 0.29 mg. per cent).

fecal excretion rose to 28 mg. on September 10, 52 mg. on September 11, and 34 mg. on September 12 (Fig. 3). The stools were semiformed on September 12, though they had not yet become solid. It was necessary to remove the infant from the metabolism frame after this date. The blood plasma values were quite low, averaging from 0.23 to 0.29 mg. per cent, and showed no rise following the large oral doses of vitamin C. Urinary excretion was low throughout.

CASE 3.—M. Y., aged 3 months, was admitted to the hospital with nonspecific diarrhea and average two to four liquid stools daily. The infant was placed on a protein milk formula, and 200 mg. of ascorbic acid were administered orally on August 23, 24, and 25. The stools contained 5 mg. of ascorbic acid on August 23,

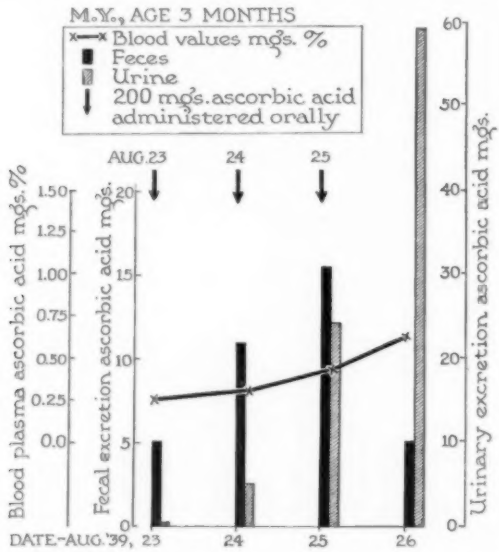

Fig. 4.—Fecal loss of ascorbic acid during diarrhea. M. Y., aged 3 months, had nonspecific diarrhea, liquid stools on August 23, 24, and 25, 1939. Stools were semisolid on August 26. The infant received 200 mg. ascorbic acid orally on August 23, 24, and 25. Stool ascorbic acid recoveries decreased as movements became formed; plasma ascorbic acid rose; and urinary excretion increased.

11 mg. on August 24, 15 mg. on August 25, and 5 mg. on August 26 (on which date the stools were definitely more formed than previously) (Fig. 4). The blood plasma in this infant rose from an initial value of 0.26 mg. per cent to 0.62 mg. per cent, and there was a considerable increase in the urinary excretion on August 26, which corresponded to the highest blood plasma value.

DISCUSSION

The experiments here reported demonstrate a considerably increased fecal excretion of ascorbic acid accompanying infantile diarrheas. Blood plasma values and urinary excretion tend to remain low even when large amounts of ascorbic acid have been orally ingested. This is in contradiction to the findings reported for the normal infant (Fig. 1). Even in the scorbutic infant, as reported by one of us[12] in 1937, the blood plasma values and urinary excretion rapidly increase follow-

ing repeated large daily oral doses of ascorbic acid. The increased fecal excretions of ascorbic acid following catharsis and during the course of diarrhea in infants point to a failure of complete absorption of the vitamin from the intestinal tract in these conditions. The possibility of increased destruction of ascorbic acid by certain organisms, either high or low, in the intestinal tract has been pointed out[5] and cannot be dismissed without further investigation. However, in these experiments the rapid diminution in fecal excretion with the appearance of formed stools points more to a failure of absorption due to increased motility than to an increased destruction by bacteria in the intestinal tract.

The failure of the blood plasma values to rise and the low urinary excretion of ascorbic acid following the ingestion of large oral doses of vitamin C corroborate the findings of an increased fecal excretion, as evidence of a failure of absorption of vitamin C in infantile diarrhea.

An interesting point is demonstrated by the final day of the experiment in Case 3, when the stools became definitely more formed. On this day, when a decrease in fecal excretion was noted, a considerable rise in the blood plasma level and urinary excretion occurred.

In the studies of Meyer and Robinson and of Chu and Sung the blood plasma levels and urinary excretions were also noted to be low and did not increase until the diarrhea abated or until ascorbic acid was administered parenterally.

The question of the development of scurvy during *acute* infantile diarrhea would hardly arise, though in protracted diarrhea this association would warrant more serious consideration.

It has been recognized,[6, 7, 13] but not generally comprehended, that the consumption of vitamin C changes with the degree of saturation of the body. In our opinion the greater utilization of vitamin C at high plasma levels is necessary for the proper physiologic function of certain essential body processes, and, conversely, during inadequate vitamin C intake at low plasma levels these activities are depressed and finally lead to the scorbutic state.

We have further noted[6] and can only re-emphasize that "*in adults scurvy usually does not occur until the blood level is much lower than that frequently occurring at the onset of scurvy in the infant or young child.*" This statement is construed to mean that an adult can exist with an extremely low plasma ascorbic acid value *for a long period of time* and show no apparent sign of the scorbutic state as has recently been so well demonstrated by Crandon, Lund, and Dill.[14] In this condition clinical scurvy eventually results and may be initiated by a superimposed diarrhea or infection.

A greater need for, or higher metabolism of, vitamin C is manifested by the young, rapidly growing infant or child as contrasted to the adult whose metabolism is at a generally lower rate not requiring the extra demands of growth.

It is our impression that normal infants, children, and adults differ considerably at various times in their response to fixed oral doses of ascorbic acid. There seem to be individual variations to the plasma level at which a considerable renal spilling of vitamin C occurs, and signs of scurvy may manifest themselves in infants at varying low plasma levels, especially when other factors precipitate the scurvy.

The clinical experience of many astute investigators is evidence for the statement that diarrheal disturbances may initiate scurvy. Aron[15] has noted that, following dysentery and diarrheal diseases, scurvy is likely to occur, not only in the infant but also in the older child. Hess[16] stated that scurvy was frequently seen in association with dysentery during the Great War and commented that this observation was referred to by many writers.

Finally Bean and Spies[17] in a recent report, stated that, while the importance of infantile diarrhea to the development of deficiency states has been little studied, a deficiency of nicotinic acid accompanying summer diarrhea has frequently been noted by them.

CONCLUSION

In a preliminary report it has been noted that ascorbic acid is excreted in small amounts in the stool of the normal infant. Large amounts of orally administered ascorbic acid were excreted in the stool of an infant following catharsis.

In three infants studied during the course of acute nonspecific diarrhea, a considerable increase of the fecal excretion of ascorbic acid is here reported. During the acute diarrhea, blood plasma values and urinary excretion tend to remain low, even when large amounts of ascorbic acid have been orally ingested. There is a rapid diminution of fecal excretion of ascorbic acid when the diarrhea abates and the liquid stools change to formed stools. These facts point to a failure of absorption of ascorbic acid from the intestinal tract during infantile diarrhea, rather than to an increased destruction of ascorbic acid by bacteria in the intestinal tract. This failure of the oral absorption of ascorbic acid during diarrhea in infancy would not be clinically significant in acute diarrhea of short duration. In protracted or chronic diarrhea in infancy the data here presented would indicate the need for the parenteral administration of ascorbic acid as a protection against the development of scurvy.

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PROTHROMBIN IN THE NEWBORN INFANT

II. Prothrombin Response to Water-Soluble Naphthoquinone Administered Intravenously

III. On the Nature of Prothrombin in the Newborn Infant

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II. PROTHROMBIN RESPONSE TO WATER-SOLUBLE NAPHTHOQUINONE ADMINISTERED INTRAVENOUSLY

INTRODUCTION

THE progress of vitamin K therapy was materially hastened with the discovery in 1939 that vitamin K possesses a quinoid structure.[1] Shortly thereafter phthiacol, having the structure 2-methyl-3-hydroxy-1, 4-naphthoquinone was synthesized and found to possess antihemorrhagic activity.[2] In 1939 vitamin K_1 was isolated from alfalfa and was found to have the structure 2-methyl-3-phytyl-1, 4-naphthoquinone.[3, 4] Since then a number of other synthetic naphthoquinones have been demonstrated as having vitamin K activity. Of these, 2-methyl-1, 4-naphthoquinone has been found to be the most potent member.[5] The clinical response to oral administration of 2-methyl-1, 4-naphthoquinone in patients with prothrombin deficiency was reported early in 1940.[6] This compound is itself relatively insoluble in water, 10 c.c. being required for the solution of 1 mg. However, a number of water-soluble naphthoquinones are now available, and their efficiency in adults when administered intravenously has been demonstrated by various investigators.[7-10] No toxic effects were observed. The intramuscular administration of naphthoquinine derivatives has been found to be less effective than either the oral or intravenous route.[12]

In hypoprothrombinemic infants Poncher and Kato[11] and Snelling[13] have pointed out that the naphthoquinone derivatives are effective in initiating a prothrombin elevation within a few hours after either oral or subcutaneous administration. The prothrombin level was reported to reach a normal value within twenty-four hours and to maintain this position thereafter. To date, the effect of intravenous administration of naphthoquinone in newborn infants has not been studied adequately.

PURPOSE OF STUDY

The purpose of the first part of this investigation was to determine the shortest duration of time required for the initial prothrombin

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elevation to become manifest in newborn infants with prothrombin deficiency, following the intravenous administration of a water-soluble derivative of 2-methyl-1, 4-naphthoquinone.

In addition, observations were made upon the quantitative character of the response at frequent intervals following this initial effect.

It was felt that this information should be of considerable value in understanding the physiologic response to naphthoquinone therapy. In the intravenous administration of a water-soluble derivative of 2-methyl-1, 4-naphthoquinone there is available a means of administering a vitamin K active substance whose effect may be closely studied, without the introduction of the variable factor of absorption from either the gastrointestinal tract or subcutaneous tissue such as oral or subcutaneous administration would involve.

TABLE I

PROTHROMBIN DETERMINATIONS ON NORMAL NEWBORN INFANTS

CASE	AGE (HOURS)	PROTHROMBIN CLOTTING TIME (SECONDS)		PROTHROMBIN CONCENTRATION (PER CENT)	
		UNDILUTED PLASMA	PLASMA DILUTED 1:1	ESTIMATED FROM UNDILUTED PLASMA	ESTIMATED FROM PLASMA DILUTED 1:1
Controls	Adult	12½	15	100	100
1	24	14	19	70	68
2	24	51	95	10	12
3	49	14	17	70	80
4	36	23½	37½	25	26
5	58	25	45	24	22
6	19	67	186	8	8
Controls	Adult	11½	14	100	100
7	24	12½	16	80	76
8	12	13	17	70	64
9	28	13	17	70	64
10	46	18	29	28	26
11	30	12	15	90	86
12	14	16	24	38	34
13	23	20	31	22	26
14	16	15	19	44	50
15	16	12½	15½	80	80
16	58	17	25	32	32
17	37	21	33	21	22
18	38	13	17½	70	60
19	27	13	17	70	64
20	8	14	19	50	50
21	48	15½	21	40	42
22	38	26	42	15	18
23	25	900+	No clot	<3	<3

METHOD OF STUDY

In this investigation the water-soluble naphthoquinone employed was 2-methyl-1, 4-naphthohydroquinone-3-sodium sulfonate.* In each case when the naphthoquinone

*This preparation was kindly supplied by Abbott Laboratories in ampules of 1 c.c. containing 3.2 mg. of the naphthohydroquinone and corresponds to 2 mg. of 2-methyl-1, 4-naphthoquinone. A dosage of 0.5 c.c. corresponding to 1 mg. of 2-methyl-1, 4-naphthoquinone was used in each case.

was administered a dosage corresponding to 1 mg. of 2-methyl-1, 4-naphthoquinone was used and given intravenously into a scalp vein. In an attempt to detect the latent period until the initial effect became apparent upon the prothrombin level, prothrombin determinations were performed at frequent intervals (some as short as fifteen minutes) following therapy.

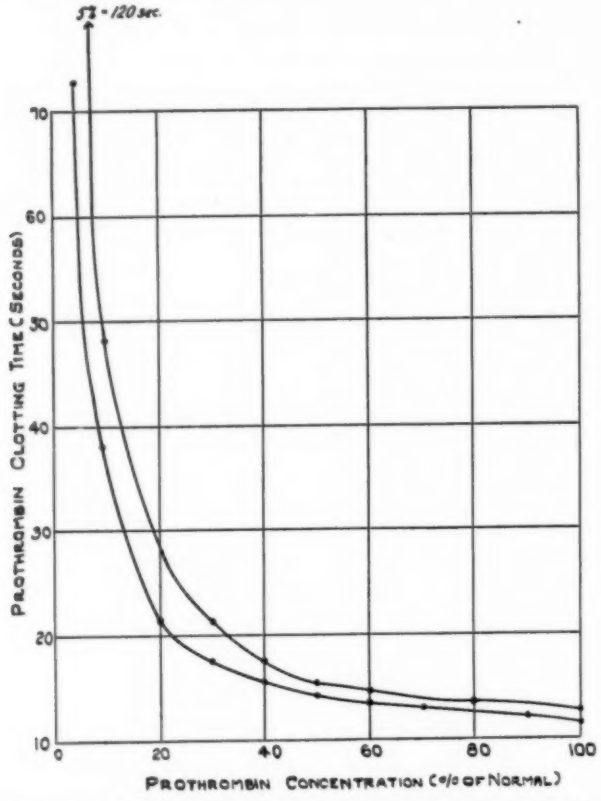

Fig. 1.—Prothrombin clotting times of serial dilutions of normal adult plasma, using thromboplastin potencies of 11.5 seconds and 12.5 seconds for the undiluted plasma.

The method of Quick[17] was employed in the preparation of thromboplastin and in the technique of prothrombin determination. Blood for the determination was obtained from either the external or internal jugular veins. The prothrombin clotting time was determined for undiluted plasma as well as for plasma diluted with an equal quantity of saline, as a check upon each other and to secure increased accuracy. The prothrombin clotting times of normal adult controls were estimated with each group of determinations. The value for the normal adult varies with the potency of the thromboplastin preparation employed. In this study the preparations yielded a value of 11.5 and 12.5 seconds. The results were expressed in terms of prothrombin clotting time as well as percentage concentration of the adult value. The latter value was determined from a graph constructed of the prothrombin clotting times of serial dilutions of normal adult plasma for each potency of thromboplastin (Fig. 1). It should be understood that this is not an absolute estimation

of prothrombin concentration, but really a summation of the concentration and its convertibility to thrombin. Results expressed in terms of both prothrombin concentration and prothrombin clotting time permit comparison of figures despite varying potencies of thromboplastin preparations.

Prothrombin studies were conducted upon a large number of newborn infants to select cases with varying degrees of prothrombin deficiency. In Table I are presented the results of prothrombin determinations upon a small group of infants merely to indicate the presence of a prothrombin deficiency in a large percentage of newborn infants, as has been pointed out by various investigators.[14-16] It is interesting to note how closely the determinations of prothrombin concentrations for undiluted plasma specimens check with those upon diluted plasma. In none of these infants was there any evidence of hemorrhagic diathesis regardless of the severity of prothrombin deficiency. This would indicate, as has been suggested previously,[16] that a prothrombin deficiency is not sufficient in itself to precipitate the picture which we associate with hemorrhagic disease of the newborn infant. Some additional factor or factors must necessarily accompany the prothrombin deficiency.

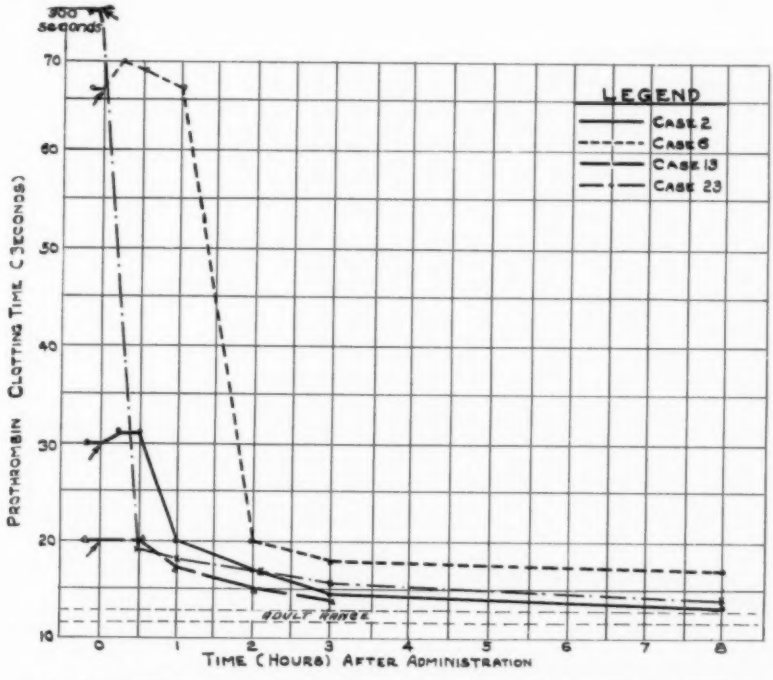

Fig. 2.—Effect of intravenous administration of 1 mg. of 2-methyl-1, 4-naphthoquinone upon prothrombin clotting time in four newborn infants with prothrombin deficiency.

RESULTS OF STUDY

Four newborn infants were chosen as representative of the various degrees of severity of prothrombin deficiency. Detailed prothrombin

studies were conducted following the intravenous administration of 1 mg. of 2-methyl-1, 4-naphthoquinone in soluble form. Table II and Figs. 2 and 3 show the results of this investigation.

From an analysis of these figures it will be seen that in all cases, regardless of the degree of hypoprothrombinemia, there was a definite prothrombin response within two hours following naphthoquinone therapy. However in the individual cases the latent period varied from within one-half hour in one case, within one hour in two cases and within two hours in one case.

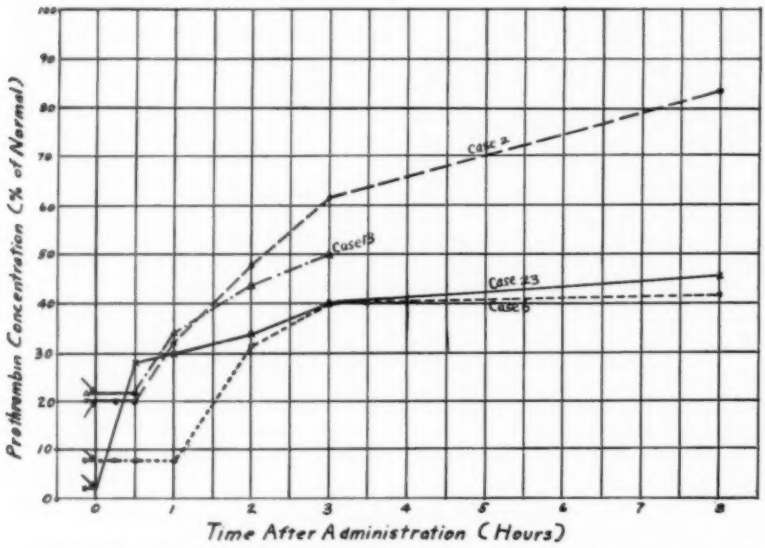

Fig. 3.—Effect of intravenous administration of 1 mg. of 2-methyl-1, 4-naphthoquinone upon the prothrombin concentration (per cent of normal) in four newborn infants with prothrombin deficiency.

Furthermore, this latent period was evidently not related to the initial degree of prothrombin deficiency. In Case 13 and Case 2 with prothrombin clotting times of twenty seconds (concentration 22 per cent) and thirty seconds (concentration 18 per cent) respectively, the initial response became manifest within one hour. In Case 6 with a prothrombin clotting time of sixty-seven seconds (concentration 8 per cent) it was not apparent until within two hours. However, in Case 23 with the most severe deficiency (concentration less than 3 per cent) and with no detectable clot formation after fifteen minutes, the effect was manifested within the short interval of one-half hour.

Following this latent period, the first response was associated with a precipitous drop in the prothrombin clotting time in those cases with the initial high clotting times, as shown in Case 6 and Case 23.

TABLE II

RESPONSE OF FOUR NORMAL NEWBORN INFANTS WITH VARYING DEGREES OF PROTHROMBIN DEFICIENCY TO INTRAVENOUS ADMINISTRATION OF 1 MG. OF 2-METHYL-1, 4-NAPHTHOQUINONE

CASE	AGE (HOURS)	NAPHTHOQUINONE INTRAVENOUSLY	TIME AFTER THERAPY (HOURS)	PROTHROMBIN CLOTTING TIME (SECONDS)		PROTHROMBIN CONCENTRATION (PER CENT OF NORMAL)	
				UNDILUTED PLASMA	PLASMA DILUTED 1:1	ESTIMATED FROM UNDILUTED PLASMA	ESTIMATED FROM DILUTED PLASMA 1:1
Normal	Adults			11½	14	100	100
13	23			20	31	22	24
		1 mg.					
	23½		½	20	30	22	22
	24		1	17	24	32	34
	25		2	15	20	44	44
	26		3	14	18½	50	50
Normal	Adults			12½	15	100	100
2	24			51	95	10	12
	48			30	46½	18	20
		1 mg.					
	48¼		¼	31	48	18	20
	48½		½	31	47	18	20
	49		1	20	32	32	32
	50		2	17	23	42	48
	51		3	14½	20½	60	62
	56		8	13	17	90	84
Normal	Adults			12½	15	100	100
6	19			67	186	8	8
	28			67	181	8	8
		1 mg.					
	28¼		¼	70	192	8	8
	28½		½	69	187	8	8
	29		1	67	190	8	8
	30		2	20	32	32	32
	31		3	18	28	38	40
	36		8	17	26	42	42
Normal	Adults			11½	14	100	100
23	25			900+	No clot	<3	<3
		1 mg.					
	25½		½	19	28	25	28
	26		1	18	26½	28	30
	27		2	17	24	32	34
	28		3	15½	21½	40	40
	33		8	14	20	50	46

The effect which followed the initial response in this study appeared to depend upon the degrees of prothrombin deficiency. In Case 2, with a moderate hypoprothrombinemia, the prothrombin concentration reached normal levels within an eight-hour period. While in Case 6 and Case 23, with severe prothrombin deficiencies, a moderate hypoprothrombinemia was still present at the end of this period of time, although well above the so-called "critical bleeding level."

III. ON THE NATURE OF PROTHROMBIN IN THE NEWBORN INFANT

PURPOSE OF STUDY

In the second part of this investigation an attempt was made to throw some light upon the question of whether the prothrombin of the newborn infant is qualitatively similar to that of the normal adult.

METHOD OF STUDY

In view of the fact that prothrombin has not been isolated in pure form, a chemical comparison is not possible. However the relative behavior of prothrombin in the mechanism of clotting in the case of newborn infants and normal adults offers a basis from which valuable conclusions may be drawn. Briefly, the theory of blood clotting involves the following process:

(1) prothrombin + calcium + thromboplastin → thrombin

(2) thrombin + fibrinogen → fibrin (clot)

The Quick method of prothrombin determination measures the summation of the factors of prothrombin concentration and its convertibility to thrombin. Investigation into the character of reaction of this summation factor in the newborn infant and the normal adult is possible by prothrombin determinations (Quick method) upon various dilutions of plasma.

If prothrombin clotting times of serial dilutions of normal adults are estimated and a graph constructed, a characteristic curve is obtained, as shown in Fig. 4. Conclusions may then be drawn from a comparison of this curve with those of serial dilutions of plasma of newborn infants under various conditions.

RESULTS

The prothrombin in infants with normal levels was first investigated. The prothrombin clotting times of serial dilutions of the plasma of Case 7 and Case 15, representing this type, were estimated, and graphs were constructed. The resulting curves were found to simulate that of a normal adult (Fig. 4 and Table III).

To determine the characteristic of prothrombin in hypoprothrombinemic infants the same procedure was followed in Case 22 and Case 16, who exhibited various degrees of prothrombin deficiency. Again the resulting curves simulated that of the normal adult, for their comparable values (Fig. 5 and Table III).

The reaction of the prothrombin produced as a result of the administration of naphthoquinone was then studied. Case 23 was chosen because no demonstrable prothrombin was present prior to the administration of the naphthoquinone. Blood was drawn two hours after the intravenous

TABLE III

PROTHROMBIN CLOTTING TIMES OF SERIAL DILUTIONS OF PLASMA OF TREATED AND UNTREATED NEWBORN INFANTS

CONCENTRATION OF PLASMA (%)	NORMAL ADULT CONTROL		INFANTS WITH FAIRLY NORMAL PROTHROMBIN LEVELS				INFANTS WITH PROTHROMBIN DEFICIENCY				INFANT WITH ALMOST ABSENT PROTHROMBIN (SPECIMEN TAKEN TWO HOURS AFTER INTRAVENOUS QUINONE THERAPY)	
			CASE 7		CASE 15		CASE 16		CASE 22		CASE 23	
	PROTHROMBIN CLOTTING TIME (SECONDS)	PROTHROMBIN CONCENTRATION (%)	PROTHROMBIN CLOTTING TIME (SECONDS)	PROTHROMBIN CONCENTRATION (%)	PROTHROMBIN CLOTTING TIME (SECONDS)	PROTHROMBIN CONCENTRATION (%)	PROTHROMBIN CLOTTING TIME (SECONDS)	PROTHROMBIN CONCENTRATION (%)	PROTHROMBIN CLOTTING TIME (SECONDS)	PROTHROMBIN CONCENTRATION (%)	PROTHROMBIN CLOTTING TIME (SECONDS)	PROTHROMBIN CONCENTRATION (%)
100	11½	100	12½	80	12½	80	17	32.0	26	15.0	17	32.0
90	12	90	12½	72			18½	28.8	28	13.5		
80		80	13	64	13½	64	20	25.6	31	12.5		
70	13	70			14	56	21	22.4	37	10.5	22	22.4
60	13½	60	15	48	14½	48	23	19.2	44	9.0		
50	14	50	16	40	15½	40	25	16.0	55	7.5	24	16.0
40	15½	40	20	32	19	32	29	12.8	65	6.0	30	12.8
30	17½	30	24	24	24	24	39	9.6	73	4.5	37	9.6
20	21½	20	31	16	34	16	59	6.4	124	3.0	53	6.4
10	38	10	57	8	53	8	140	3.2	202	1.5	118	3.2
5	73	5	105	4	116	4						

administration of 1 mg. of 2-methyl-1, 4-naphthoquinone, and the prothrombin clotting times of serial dilutions of the specimens of plasma were estimated. Again it was found that the resulting curves simulated that of the normal adult as well as that of untreated infants with their natural prothrombin (Fig. 5 and Table III).

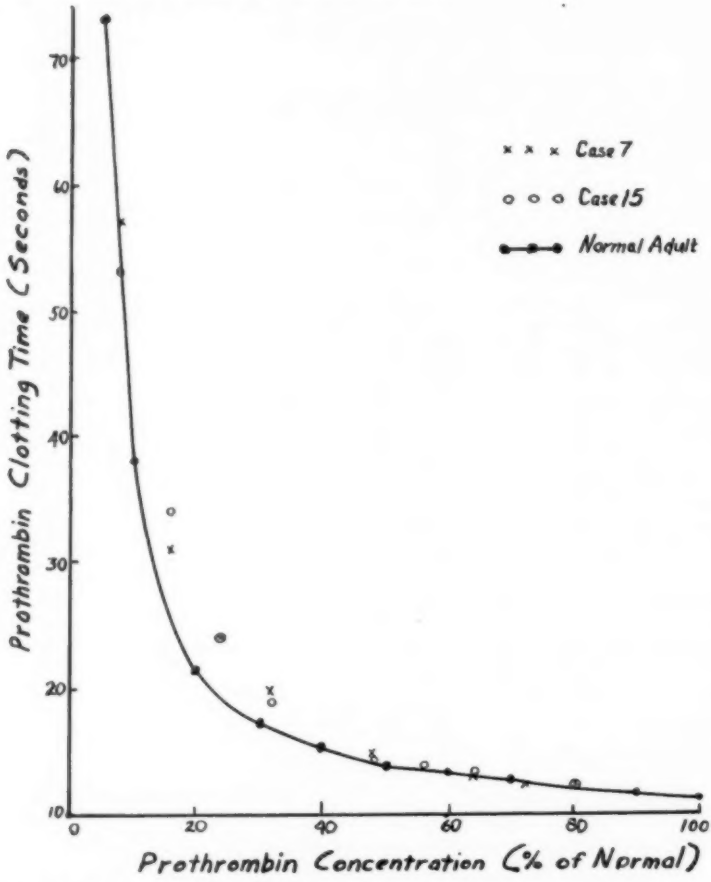

Fig. 4.—Graphs of prothrombin clotting times of serial dilutions of plasma of untreated newborn infants with fairly normal initial levels of prothrombin.

These findings demonstrate, first, that the summation of the factors of prothrombin concentration and its convertibility (to thrombin) in the clotting mechanism is similar in the adult and in the newborn infant, regardless of the presence or absence of hypoprothrombinemia. Second, the summation of these factors in newborn infants is the same whether the prothrombin be of natural origin or produced as a result of naphthoquinone therapy.

These data supply presumptive evidence that the prothrombin of the newborn infant qualitatively simulates that of the normal adult. Furthermore, this qualitative similarity exists irrespective of the original concentration or source of the prothrombin.

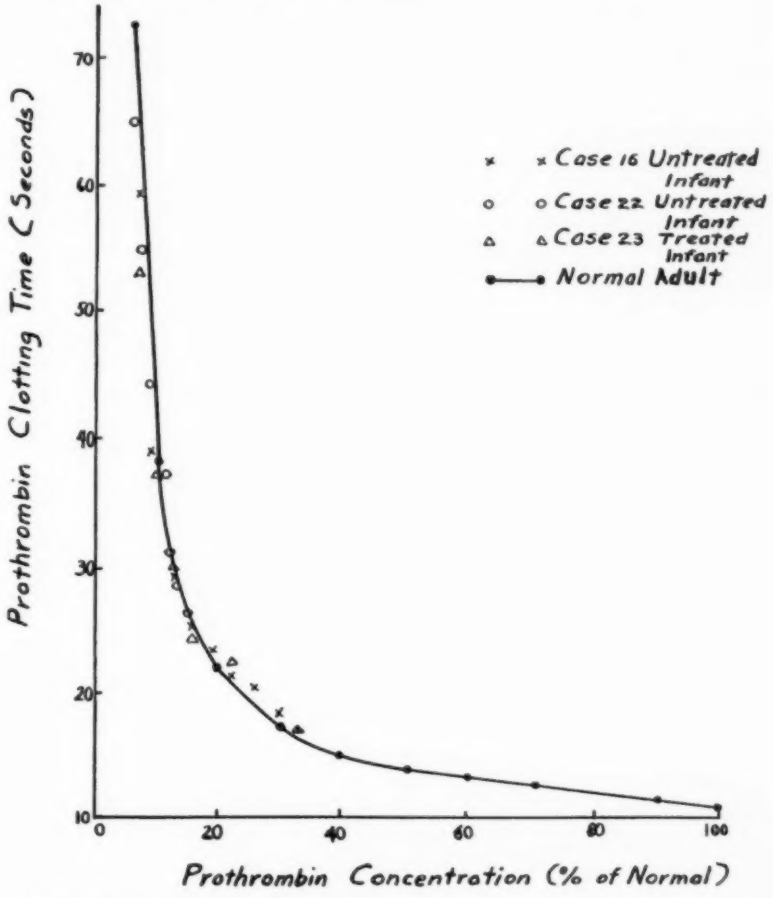

Fig. 5.—Graphs of prothrombin clotting times of serial dilutions of plasma of untreated hypoprothrombinemic newborn infants and one following intravenous administration of 1 mg. of 2-methyl-1, 4-naphthoquinone.

COMMENT

The character of the response which follows the administration of 2-methyl-1, 4-naphthoquinone in newborn infants with prothrombin deficiency has an important practical bearing upon the problem of treatment in cases of hemorrhagic disease of the newborn. In infants with recent onset of hemorrhagic phenomena and where only mild oozing is present, it may be adequate to administer intravenously 1 mg. of a

soluble form of 2-methyl-1, 4-naphthoquinone, with the knowledge that the prothrombin response may be expected from within one-half to two hours. In these cases no harm can follow even if the initial effect is not manifested until two hours after the administration of the naphthoquinone. However, preparations for immediate transfusion should be made following the administration of naphthoquinone because of the danger of a sudden increase in bleeding at any time prior to the initial prothrombin response. If this latter phenomenon should not occur, transfusion may be withheld.

However, in those infants where oozing has continued for some time, or where bleeding is more profuse, it is not sufficient to administer vitamin K intravenously and await the prothrombin response. One cannot foretell whether an individual case will respond within one-half hour or only within two hours or whether the critical bleeding level will have been passed with the initial prothrombin response. In a severe case a delay of two hours may result in a fatality. In these infants vitamin K therapy in the form of 1 mg. of 2-methyl-1, 4-naphthoquinone in soluble form intravenously should be supplemented by a transfusion. The latter offers an immediate source of prothrombin, and the vitamin K will result in the rapid manufacture of prothrombin and the maintenance of its elevated level. Certainly, infants with appreciable hemorrhage should receive a transfusion as an adjunct to vitamin K therapy to replace blood loss. Of course the naphthoquinone may be administered orally with good results, but the response may be expected to be somewhat slower and more unpredictable because of the uncertain factor of absorption.

SUMMARY

1. Four newborn infants were chosen as representative of the various degrees of severity of hypoprothrombinemia.

2. Detailed prothrombin studies were performed upon the plasma of these infants at short intervals following the intravenous administration of a water-soluble form of 1 mg. of 2-methyl-1, 4-naphthoquinone.

3. In all cases there was a definite prothrombin response within two hours after therapy.

4. In the individual cases the interval from the time of administration of the naphthoquinone until the initial effect became apparent upon the prothrombin level was found to vary from within one-half hour to two hours.

5. In the infant with only moderate prothrombin deficiency the prothrombin level reached a normal value within eight hours, while those with severe deficiency were still somewhat hypoprothrombinemic at the end of this period of time.

6. The nature of the prothrombin of the newborn infant was investigated to determine its similarity to that of the normal adult.

7. This was accomplished by comparing the graphs constructed of the prothrombin clotting times of serial dilutions of plasma of normal adults and newborn infants under various conditions.

8. These resulting curves for infants with normal prothrombin deficiency were similar to that of the normal adult.

9. A similar curve was obtained for a newborn infant whose prothrombin was produced as a result of naphthoquinone therapy.

10. These similarities offer presumptive evidence that the prothrombin of the newborn infant is qualitatively similar to that of the normal adult regardless of its concentration or source.

11. Transfusions as an adjunct to vitamin K therapy are important in certain types of cases of hemorrhagic disease of the newborn infant.

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TETANY FOLLOWING SODIUM CHLORIDE REPLACEMENT THERAPY

Report of Unusual Case

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SINCE the report, "On the Relation of Tetany to the Parathyroid Glands and to Calcium Metabolism," by MacCallum and Voegtlin,[1] there has been a large amount of literature on the subject of tetany, particularly concerning its etiology and treatment. However, we have been unable to find any report of a case of tetany developing under the conditions manifested by the following patient:

Case 431003.—A 15-year-old boy was admitted to the medical service with the chief complaint of persistent vomiting for the previous three weeks. The history from his parents and referring physician was that of multiple recurrent attacks of nausea and vomiting since birth, resistant to therapy, and producing a chronically emaciated, gangling boy. The present attack commenced with the sudden onset of nausea, vomiting, and pain in the right lower quadrant, the latter feature not having been present with the former attacks. Ten days after the onset of the present illness an appendectomy had been performed and revealed a normal vermiform appendix, but the pylorus was thickened and the mesenteric glands were enlarged. A biopsy of the latter showed only chronic hyperplastic lymphadenitis. Vomiting and malaise continued, and the boy was referred to the University Hospital.

Physical examination revealed a very emaciated boy of normal stature, but of inadequate muscular development. His intellectual acuity was somewhat dulled, but he answered direct questions and was cooperative. Clinical signs of moderate dehydration were present. Heart and lungs were normal. There was a healing right midrectus surgical incision which was moderately tender. There was slight abdominal distention; otherwise the physical findings were normal.

A period of observation was advised, and correction of the dehydration was instituted. Five days after admission, after a total of 9,200 c.c. of water by mouth, 2,000 c.c. of normal saline and 3,000 c.c. of 5 per cent glucose solutions intravenously had been given, a plasma chloride determination was reported by the central laboratory as 182 mg. per cent calculated as sodium chloride. This was the lowest plasma chloride level ever obtained at the University Hospital. The specimen had become hemolyzed, however, so the finding must be interpreted as though it were a whole blood determination (normal value: 450 to 500 mg. per cent). To combat this deficiency, 3,000 c.c. of Ringer's solution (7.5 Gm. of NaCl per liter) were given during the fifth day. The following day a plasma chloride determination on an unhemolyzed specimen was found to be 248 mg. per cent (normal value: 560 to 600 mg. per cent); and the carbon dioxide combining power was 99 volumes per cent (normal value 50 to 70 volumes per cent). This would seem to indicate that the whole blood chloride value of 182 mg. per cent the previous day was not far wrong. The administration of 6,000 c.c. of Ringer's solution during the next two days resulted in a rise of the plasma chlorides to but 330 mg. per cent and

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reduced the carbon dioxide combining power to 86.8 volumes per cent. At this time an upper gastrointestinal x-ray examination showed complete obstruction of the second portion of the duodenum from an indeterminate cause, and the patient was transferred to surgery, where "electrolyte balance studies" were started. Using the formula*[2] developed in this clinic for the determination of the amount of sodium chloride solution needed by a patient deficient in this substance, it was found that the boy required 35.8 Gm. of salt to correct the deficit. This was administered as 5,000 c.c. of Ringer's solution and caused a marked clinical improvement, although an excretion of 16.1 Gm. of salt occurred in the urine during this twenty-four-hour period. It was decided that relief of the duodenal obstruction was indicated, and the following day operative correction of a torsion of the colon around the duodenum was accomplished. Each day for the next five days the boy was given the amount of salt calculated through the use of the formula as needed for restitution of the plasma chloride concentration to the normal level. He excreted it in the urine as rapidly as it was administered. On the sixth day of the study he was given almost twice the computed necessary amount of salt without its producing appreciable effect on his plasma chlorides, and the attempt at restitution beyond 467 mg. per cent was abandoned. At that time the carbon dioxide combining power was 73.9 volumes per cent.

A soft diet was started, and clinical improvement was rapid. In three days he was shifted to a general diet, and his plasma chlorides rose, without any salt therapy, to 518 mg. per cent. On the morning of the tenth postoperative day the boy complained of stiffness of his hands and inability to pick up objects. Examination revealed bilateral carpal spasm with the typical accoucheur's hand. There was no pedal spasm present. Chvostek's and Trousseau's signs were both easily demonstrable. No history of hyperpnea could be obtained, and the patient was not hyperventilating during the prolonged period of questioning and examination. There had been no upper gastrointestinal losses for the previous eight days, and the salt content of the preceding losses had been more than amply replaced. Blood chemistry studies at the time of the tetany showed a plasma chloride concentration of 543 mg. per cent, carbon dioxide combining power of 55.6 volumes per cent, and a serum calcium of 10.0 mg. per cent (normal value: 9 to 11 mg. per cent). Since the spasm was not particularly discomforting, therapy was postponed to observe the clinical course of the condition. The spasm continued with only moderate relief, and at the end of the next six days it was thought that spontaneous cure was not going to occur. The boy was then placed on a regime of ammonium chloride, 1 Gm. four times a day. During the next three days a gradual relaxation of the excessive muscular tone occurred, and the hands became entirely normal. When he was discharged three days later, his plasma chlorides were 568 mg. per cent and the carbon dioxide combining power was 50.2 volumes per cent. He was completely free of any tendency toward tetany and has been well to date.

DISCUSSION

This patient presented several interesting conditions for which we were unable to account. On admission his plasma chloride level was 182 mg. per cent, which is extremely low. Up to this time it had been our experience that patients with plasma chlorides approaching 250 mg. per cent were stuporous; this boy answered direct questions and was cooperative.

*For each 100 mg. per cent that the plasma chlorides need to be raised to reach the normal of 560 mg. per cent, the patient should be given 0.5 Gm. of sodium chloride per kilogram of body weight.

A second unusual point at the time of admission was the absence of any symptoms of tetany in the presence of a marked degree of alkalosis as indicated by plasma chlorides of 182 mg. per cent and a carbon dioxide combining power of 99 volumes per cent. A paradox, however, was the development of tetany on the tenth postoperative day, after the plasma chloride and carbon dioxide combining power had returned to normal, after the boy had been eating a fair diet for four days, and when the serum calcium was normal. Tetany usually results from one of two conditions: (1) a reduction of the physiologically active serum calcium, as in infantile tetany, or produced by the intravenous injection of dibasic sodium phosphate and the subcutaneous injection of sodium oxalate, or (2) tetany occurring with alkalosis, which seems to be related to the quantity of ionized calcium rather than the total blood calcium. We cannot explain the unusual features in this case. We do regret that other blood chemistry studies, such as serum sodium, were not done at the time of the boy's abnormalities. The lack of tetany at the initial period and its development later were occurrences which will keep us searching for similar cases or the reported experiences of others.

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NEONATAL CORTICAL INSUFFICIENCY (ADDISON'S DISEASE) ASSOCIATED WITH THE ADRENO-GENITAL SYNDROME

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THE simultaneous appearance in an infant of symptoms indicating deficiency of one and hypersecretion of another hormone of the adrenal cortex is of interest as a clinical syndrome and also of significance in the light it sheds on the physiology and possibly on the anatomy of the adrenal cortex. The appearance in the literature of three articles dealing with the subject, during the year that we were following an infant with the symptom complex, has been particularly interesting and illuminating. There is still much to be learned about this congenital condition and many ramifications to be traced before our knowledge of the syndrome is complete, but a picture is beginning to emerge.

It seems logical to introduce the cases from the literature as they came to our attention during the evolution of the disease in our own patient.

R. M., a male child, the third of normal, healthy, Italian-American parents, was born on Nov. 18, 1939, weighing 7 pounds 10 ounces. The first child of the family, a boy of 10 years, is living and well; the second child, who was born in 1935, died at 5 weeks of age with symptoms similar to those of our patient. The birth of R. M. was abnormal only in that the cord was wound tightly around the neck three times. Resuscitation was not difficult, but the face remained discolored for about three days. The baby was given 20 c.c. of whole blood intramuscularly from the mother the day after birth. The child was put to breast according to hospital routine every three hours in the day and every four hours at night. The mother had an abundant milk supply, and the infant nursed well but failed to gain and later lost weight. For this reason a supplementary formula was started on the seventh day. On the eighth day the weight dropped an additional 5 ounces, and the stools became frequent and green and contained large amounts of mucus. The baby was isolated immediately; normal salt was given by clysis; and a change of formula made. Stool cultures revealed no pathologic organisms to explain the diarrhea, and the subsequent character and consistency of the movements did not suggest an infectious origin. There was no fever. The child took his food poorly, vomited frequently, and was very listless. Diets with and without breast milk and various formulas were tried to no avail. Transfusions, intravenous glucose, and normal saline by clysis were necessary to sustain him. When parental fluid was omitted for one period of thirty-six hours, the patient went into collapse requiring oxygen and stimulants as well as fluids. A gastrointestinal series was done to rule out partial obstruction, such as stenosis or volvulus.

After two weeks of therapy the patient's apparent daily need of parenteral saline suggested the possibility of adrenal insufficiency as the underlying pathology. A more careful inquiry then revealed that the other infant in the family had died of symptoms similar to those of R. M. Dr. A. Sinclair had made the diagnosis of probable adrenal insufficiency but was unable to confirm his impression since the family refused permission for an autopsy. The child had a hypospadias and may have been a pseudohermaphrodite.

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TABLE I

LOG OF R. M.

DATE	WEIGHT (LB.-OZ.)	FLUID	DRUGS	REMARKS
11/18/39	7-10		1 c.c. klotogen	Living male; cord 3 times about neck; cyanosis; carbogen given; resuscitation not difficult
11/19/39	7-6	20 c.c. blood		Cyanosis of face persists; water and 5 per cent glucose 1 to 2 oz. q. 4 hr.; no vomiting
11/20/39	7-4			To breast, nursed well; color improved
11/21/39	7			To breast q. 3 hr. day; q. 4 hr. night; nursed well
11/22/39	6-15			Getting 2 to 3 oz. from breast; no vomiting; stools o.k.
11/23/39	6-14			Nursing well
11/24/39	7			Nursing well; 4 yellow stools
11/25/39	6-15			Nursed fairly well; took only 1 or 2 oz. formula
11/26/39	6-14			Nursed fairly well, breast and formula; no vomiting; 6 stools, several loose
11/27/39	6-9	100 c.c. N.S.		Regurgitating; frequent green stools; isolated; change of formula
11/28/39		100 c.c. N.S.	Kaopectate	
11/29/39	6-8	100 c.c. N.S.		Seems cold; T, 98.8° F.; sleeps all the time; difficult to arouse; stools loose and frequent; stool culture negative; salt and water by mouth
11/30/39	6-6	100 c.c. N.S.		Taking food poorly; vomiting
12/ 1/39		20 c.c. blood		
12/ 5/39	6-4	100 c.c. q.d.		Saline by mouth; ascorbic acid started; stomach wash
12/ 6/39		100 c.c. N.S. and glucose; 50 c.c. blood T.		Poor color; weak cry; rapid respirations
12/ 7/39 to 12/12/39		200 c.c. N.S. q.d.		Betalin started; formula modified; diagnosis of probable adrenal insufficiency
12/13/39	6-7	100 c.c. N.S.		G. I. Series revealed no obstruction
12/15/39		100 c.c. N.S. and 17 c.c. serum		
12/16/39		No clysis		
12/17/39		Glucose and 100 c.c. N.S.	Caffeine, adrenalin, and oxygen	Collapse; history of sibling obtained
12/18/39 to 12/27/39	6-8	Clysis q.d.	1/10 grain thyroid	Fever one day; stools better; blood sugar 74 mg. per cent; whole blood chlorides 441 mg./100 c.c.
12/29/39	6-7		0.2 c.c. percortin	Saline and water in equal parts in formula
12/30/39 to 1/ 6/40	7		0.3 c.c. percortin	Urine chlorides 1.93 Gm. NaCl in 24 hr.
1/ 6/40 to 1/13/40	8-1		0.3 c.c. percortin	

TABLE I—CONT'D

DATE	WEIGHT (LB.-OZ.)	FLUID	DRUGS	REMARKS
1/14/40			0.2 c.c. percortin	
1/15/40	8-1		Percortin discontinued	Taking breast milk 16 oz. and formula 17 oz.; negative Wassermann test
1/18/40				Taking food poorly; regurgitating
1/19/40	7-13		Percortin restarted	Still regurgitating some
1/22/40	8		0.3 c.c. percortin	Regurgitating
1/23/40 to 1/29/40	7-15 8-1	150 c.c. N.S.	0.3 c.c. percortin	Liquid stools; urine chlorides 3.34 Gm. NaCl in 24 hr.
2/ 3/40	8-11		0.2 c.c. percortin	
2/ 8/40	9-8		0.1 c.c. q.d.	
2/12/40	10-2		Discontinued	
2/14/40				Regurgitated twice
2/15/40 (3 mo.)	10-3		No percortin	Took feedings only fairly well; regurgitated; very sleepy. Blood for Na and K taken
2/16/40	10-2		Percortin restarted	Regurgitating; very sleepy
2/17/40	9-11	150 c.c. N.S.	0.2 c.c. percortin	Formula taken poorly; still regurgitating
2/19/40	10-5		0.2 c.c. percortin and cortisorbate	Stools loose
2/20/40			Cortisorbate, percortin by mouth	
2/22/40	10-6		Cortisorbate tablets and 0.1 c.c. percortin on tongue	
2/23/40			0.1 c.c. (H)	Regurgitating; taking food poorly
2/25/40		100 c.c. N.S.	0.1 c.c.	Regurgitating; food taken poorly
2/27/40	10-12		0.2 c.c. percortin, adrenotropic factor 0.2 c.c.	
3/ 1/40 to 3/13/40	12-7		0.1 c.c. percortin, 0.2 c.c. adrenotrop, DC above	Normal salt by mouth; regular diet for age
3/15/40	12-11			T, 102° F.; respirations, rapid; drowsy; eating poorly
3/17/40	12-15			Taking food slowly, but no change made
3/19/40 (4 mo.)				Doing fairly well without medication

TABLE I—CONT'D

DATE	WEIGHT (LB.-OZ.)	FLUID	DRUGS	REMARKS
3/20/40	12-11			Eating well; no vomiting
3/22/40	12-9			Sent home
4/22/40 (5 mo.)	13-1	150 c.c. N.S.		Returned to hospital because of vomiting, fever, and irritability; Hbg. 87; W.B.C. 36,000; Polymorphonuclears 57
4/26/40				Hbg. 77; W.B.C. 14,000; Polymorphonuclears 46 per cent.
4/27/40	13-7	150 c.c. N.S.		Saline by mouth
4/29/40	13-1	150 c.c. N.S.	0.1 c.c. percortin	
4/30/40		150 c.c. N.S.	Percortin	
5/ 1/40	13-3	150 c.c. b.i.d.	0.3 c.c. percortin	X-ray sella turcica negative
5/ 9/40			Percortin	24 hr. specimen urine NaCl 1.46 Gm. in 24 hr.; K 223 mg. in 24 hr. Intake of sodium 7.5 Gm.
5/22/40 (6 mo.)	15-5		0.2 c.c. percortin	Cortalex tablets, 2 daily
6/ 1/40			0.3 c.c. percortin, growth hormone 0.2 c.c. q.d. for 5 days	Cortalex tablets, 2 daily
6/ 6/40	15-15		0.3 c.c. percortin	Cortalex tablets, 2 daily
6/12/40	16-8		0.3 c.c. percortin	Cortalex tablets, 2 daily; sent home
7/ 1/40	21-14		Percortin gradually decreased	Genitalia enlarged; cortalex continued
8/12/40 (9 mo.)	21-14		0.15 c.c. percortin every other day	Cortalex continued; pubic hair present
8/25/40			Percortin	Cortalex continued; fever vomiting; restless; admitted to hospital
8/27/40	23		Percortin Desoxycorticosterone acetate, 2 drops under tongue q.i.d.	Diagnosed exanthem subitum. Height, 74 cm.; sitting height, 46 cm.; span 72 cm.; bi-iliac, 12 cm.; penis 5 cm. Bone age: Pelvis, left wrist, and foot: "The epiphyses for the heads of the femur are of excellent size (usually appear 9-11 mo.). The capitate and hamate bones of the wrist are present but the distal epiphysis of the radius is absent (usually occurs 6-8 mo.). The distal tibial epiphysis is well developed, and the external cuneiform is present. These usually occur at 1 year of age." Intravenous pyelogram: "There are no obvious anomalies." Blood pressure 106/68; all other medication stopped; dismissed after several days on drug

TABLE I—CONT'D

DATE	WEIGHT (LB.-OZ.)	FLUID	DRUGS	REMARKS
9/23/40	19-6		Desoxycorticosterone acetate, 10 drops q.d.	Lost 3½ pounds; vomiting several times daily; wan and haggard; penis large; pubic hair present
10/ 7/40	20-6		Desoxycorticosterone acetate, 10 drops q.d.; increased to 15 drops daily	Restless; eating better; craves water
10/21/40	19-6			
10/28/40	19-11		Increased to 18 drops daily	
11/ 4/40	20-6		18 drops daily	Much better; taking less water; sleeping better
11/18/40 (1 year)	22-4		18 drops daily	Doing well
12/ 9/40	22-14		15 to 18 drops daily	0.1 c.c. Pertussis vaccine given
12/23/40	23-4		15 to 18 drops daily	0.25 c.c. Pertussis vaccine given; no reaction
12/30/40	23-12		15 to 18 drops daily	1 c.c. Pertussis vaccine given; no reaction
1/ 6/41	24-12		15 to 18 drops daily	1 c.c. Pertussis vaccine given; no reaction; child is happy, starting to walk, eats well, sleeps well
1/18/41 (14 mo.)	24-12			Measurements—Height, 82 cm.; bi-iliac, 13 cm.; span, 77 cm.; penis, 7 cm. Bone age: "Films were obtained of the shoulders; the epiphysis of the head of the humerus and also the greater tuberosity are well developed and usually do not appear until age two. "At the wrist, the capitate, hamate, and distal epiphysis of the metacarpals and phalanges are present; the latter usually appear at age three. "The right ankle and foot show that the epiphyses for the metatarsals and the internal cuneiform are present and these usually do not appear until age three. "Impression: There is definite advancement in the bone age, indicating age three." The electrocardiogram is shown in Fig. 1. Serum sodium is 297 mg. 90; serum potassium is 30.8 mg. per cent.

Blood samples for sodium and potassium studies on R. M. were taken but unfortunately hemolysis occurred, and the results were invalidated. Administration of percortin was started on December 29, and 0.3 c.c. was given hypodermically daily. As may be seen from the log, his progress from then on was considerably better except when we resorted to experimentation. Since we had no precedent to guide us and did not know whether or not repair could be expected, we tried successively gradual reduction of the dosage of percortin, administration of adrenotropic hormone to stimulate the adrenal cortex, use of salt in the diet, etc. Always, however, we had to resort eventually to subcutaneous saline and percortin given hypodermically to restore him to balance. Therefore, the mother was taught to give the drug injections at home, and he was dismissed to be followed in the outpatient department.

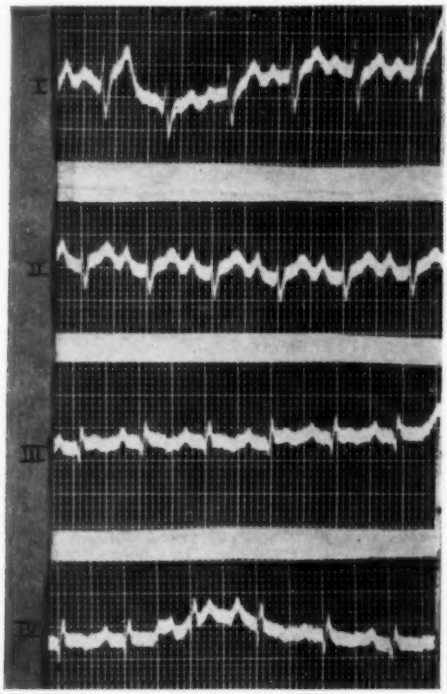

Fig. 1.—Electrocardiogram of R. M., aged 14 months, made Jan. 18, 1941.

In December, 1939, the article by Butler and his associates[1] on adrenal insufficiency and macrogenitosomia strengthened our diagnostic uncertainty and also caused us to watch our patient for abnormal genital development. There was some question at this time as to whether or not the penis was large but the consensus was that its size was within normal limits. At 6 months of age the enlargement was unmistakable and commented upon by the mother; pubic hair and a low voice were noted shortly thereafter.

In March, 1940, Wilkins and his co-workers[2] described their case of macrogenitosomia with adrenal insufficiency and bilateral hypertrophy of the androgenic zone of the adrenal glands. Their patient had had an abnormal craving for salt since early infancy and died in the hospital upon withdrawal of salt for several days. Their discussion gave us a clearer concept of the probable pathology in our own case.

In August, 1940, at 9 months of age our patient, R. M., was again admitted to the hospital because of vomiting and fever. A diagnosis of exanthem subitum was made, and recovery was uneventful. At this time another attempt to study the sodium and potassium of the blood again failed because of hemolysis. An intravenous pyelogram revealed no abnormalities in the kidneys. Bone age studies showed the lower, but not the upper, extremities to be advanced.

While the patient was in the hospital, desoxycorticosterone acetate for sublingual administration was supplied by Dr. Evelyn Anderson,[3] and the patient was started on 2 drops under the tongue four times daily (4 drops = 1 mg.). This dosage subsequently was increased to five times daily and finally to three drops five or six times a day. It is probable that, due to salivation with teething, the infant absorbs less than an adult and therefore apparently requires a larger dose. The child has remained well; he has gained weight regularly; and he has had a good appetite. When the new method of administration was first tried, he was restless and consumed, at times, excessive quantities of water. We now have determined that with these symptoms he needs more of the drug, and the mother varies the amount given accordingly.

At 14 months of age R. M.'s weight was 24 pounds 12 ounces; height, 82 cm.; bi-iliac crest, 13 cm.; anteroposterior and lateral chest, 11/16 cm.; sitting height, 50 cm.; span, 77 cm. The penis was 7 cm. long, and some pubic hair was present. His bone age was that of a 3-year-old child. His fontanel was closed. He had only four teeth. He walked holding on to objects, said a few words, and was bright and alert. When getting adequate desoxycorticosterone acetate, he was happy, but, if dosage was reduced, he was restless and irritable, had a poor appetite, and drank excessive amounts of water, 10 or 15 ounces daily. Even at these times he had no craving for salt; we have given him the opportunity to show such a preference innumerable times since early infancy. His diet was regular for his age and well fortified with vitamins. He showed no abnormal trends in his appetite except that he rather consistently refused sweet foods. This was not marked enough to attribute it to a peculiarity of his disease, although such a possibility must be considered since disturbed carbohydrate metabolism may be associated with adrenal pathology.

In May, 1940, Dijkhuizen and Behr[4] reported two cases of their own and two other cases of adrenal hypertrophy in infants. They mentioned

the condition as a new syndrome. They describe the vomiting, diarrhea, and dehydration; in all the cases intestinal obstruction was considered, and in one laparotomy was performed. At autopsy the adrenals weighed from 22 to 34 Gm. The authors were at a loss to explain the symptoms in the presence of hypertrophy of the adrenal cortex. Reports from the American literature of patients surviving beyond infancy explain the symptoms and findings. The authors cited seven other cases of adrenal hypertrophy in infants; the data were obtained chiefly from pathologic reports.

Fig. 2.—R. M. at age of 14 months.

It must be recognized, therefore, that congenital adrenal insufficiency associated with hypertrophy of the adrenal cortex exists and that death usually occurs with symptoms of gastrointestinal disturbances predominating. In the female child with this pathology pseudohermaphroditism may be present at birth; in the male child the secondary changes are not so obvious and may not be apparent unless the infant survives to several months of age.

From studies of the recorded cases, with due allowance made for the paucity of material, symptoms and findings may be temporarily summarized.

SYMPTOMS

The symptoms may be divided into those produced by adrenal cortical insufficiency and those caused by excess androgen production. The symptoms of adrenal cortical insufficiency in the infant parallel those of the adult with Addison's disease as well as those of animals subjected to adrenalectomy. These are loss of appetite, vomiting, diarrhea, weakness, anuria, rapid pulse, cyanosis, and extreme dehydration. The vomiting has repeatedly suggested partial obstruction. The dehydration has been described as resembling that of cholera. The infant may die in convulsions; in collapse with low temperature, extreme weakness, and coma; or in marasmus. With varying degrees of deficiency, there may be a modification of symptoms; the patient may have alternating diarrhea and constipation; occasionally there is increased hunger. The patient may show restlessness, thirst, salivation, and probably, at times, elevated temperature.

Pigmentation of the skin and mucous membranes, although not always present, has been described.

The second group of symptoms is due to hypersecretion of androgen. In the female this produces masculinization and pseudohermaphroditism. The clitoris is enlarged; there is a persistent urogenital sinus into which the vagina opens; and a definite prostate above and around the urethra may be present. The patients have been mistaken for males with a hypospadias. The relation of this type of case to female pseudohermaphroditism without adrenal insufficiency will be referred to again under etiology.

In the male, the results of increased androgen production may not be obvious at birth. A slight elongation of the penis is not easily detected. In infancy, furthermore, genital hypertrophy is sometimes present due to sex hormones from the mother. After the first few months, however, the penis is noticeably enlarged; pubic hair appears; the voice becomes rather deep; and there is an advancement in bone age. The testes may not enlarge to correspond to the secondary changes.

LABORATORY FINDINGS

Much remains to be done on the laboratory studies of adrenal insufficiency in infants. Specimens of either blood or urine are collected with difficulty. The margin of safety for deprivation of water and of hormones is probably small, and the well-being of the child demands a minimum of experimentation. Studies so far would indicate that the findings parallel those of adults with Addison's disease. The blood count is normal except for evidence of concentration when suffering from deficiency and consequent dehydration. The serum sodium is low; the serum potassium relatively is high; and the serum chlorides are reduced relatively less than the sodium. The excretion of sodium in the urine is

increased, but other changes occur only later after damage to the kidney has resulted. Early in the disease blood cholesterol, blood phosphate, nonprotein nitrogen, and blood glucose are normal. Alterations occur with damage to the kidneys and the liver.

The androgen excretion is high. In the cases studied it has equaled that of an adult man. In normal infants the amount secreted is insignificant.

The bone age has been advanced in the males studied.

PATHOLOGY

The pathology of the condition is obscure. The number of cases thus far investigated are few, and methods for studying these have been inadequate. Only one case has been carefully studied pathologically.[2] In this case and according to the reports from Scandinavia, the adrenals showed bilateral, marked hypertrophy of the cortex.

The anatomy of the adrenals has been exhaustively reviewed by Grollman,[5] Young,[6] Broster and Vines,[7] Benner,[8] and others. Although it has been disputed even to a recent date, it is now fairly generally agreed that the cortex of the adrenal comprises two tissues. One of these tissues, the interrenal cells, produces a hormone which is essential to life and the absence of which results in the syndrome known as cortical insufficiency or Addison's disease. The other, the androgenic tissue, has a function related to the reproductive system. In the human the androgenic tissue is present in the fetus, both male and female, but disappears rapidly after birth and is almost entirely absent at the end of the first year. Involution begins soon after birth and reaches a maximum in the second week of life. At times this normal involution has been mistaken for adrenal hemorrhage. The degenerating androgenic tissue is sharply marked off from the rest of the cortical tissue and from the medulla. The androgenic zone is gradually replaced by connective tissue to form a layer separating the medulla from the cortex. In case of hypertrophy of the androgenic tissue it is impossible, however, by ordinary microscopic stains to distinguish between these cells and other cortical cells. By means of the Ponceau-Fuchsin stain, Broster and Vines were able to study the cells. Wilkins and his associates also used this stain in studying their case and apparently found it valuable. Others have not found the stain a reliable method for differentiating cells. Differential staining, however, will probably eventually clarify the anatomy of the adrenal cortex unless indistinguishable cells secrete more than one hormone. From the evidence available at present, the symptomatology of neonatal adrenal cortical insufficiency with the adrenogenital syndrome is due to simple hypertrophy of the androgenic tissue of the adrenals and atrophy or absence of the interrenal cells. The hyper functioning of the androgenic tissue has a masculinizing effect producing, when it occurs in embryonic life in the female, pseudoher-

maphroditism. The abnormality may be so marked that the infant female is mistaken for a male with hypospadias. Such errors have been detected either at operation or on autopsy. If the individual survives, the ovaries later show hypoplasia and cystic degeneration. It is interesting to note that frequently female pseudohermaphrodites have been brought up as girls until they reach adolescence and then have changed their lives to continue as boys. The early stimulation followed by gonad degeneration may explain the increased masculinization of these females. In the male, androgenic hyperplasia produces an early development of the male secondary characteristics—macrogenitosomia, pubic hair, low voice, and advanced bone age. The male gonads like those of the female may show hypodevelopment.

Wilkins and his associates attributed the concomitant disappearance of the cortical hormone of the interrenal cells to overgrowth of the androgenic tissue. This assumption, although the most obvious, may not be correct. That there may be variations in the amount of functioning interrenal tissue available for hormone is suggested by the reported cases. The patients of Dijkhuizen and Behr did not survive beyond infancy; Wilkins' patient survived temporarily on salt alone; our patient, if the pathology is the same, needs cortical hormone to keep him alive. This suggests that there may be cases of androgenic hypertrophy without cortical deficiency and raises the question whether or not the female pseudohermaphrodites who have marked hypertrophy of the androgenic zone without any symptoms of cortical insufficiency belong in this group etiologically. From a review of the literature it appears that the occurrence of bilateral adrenal hypertrophy with macrogenitosomia in the male is extremely rare. There may be, therefore, a developmental pathology in these cases more fundamental than simple destruction of one group of cells by overgrowth of another group.

ETIOLOGY

The etiology of the syndrome described is obscure. The family incidence of it cannot be ignored. Wilkins and his associates in their review of the literature cited their case as the eleventh instance of multiple cases in a family; our own case and that of Dijkhuizen and Behr add two more families with the pathology in more than one of the progeny.

To call a condition like this hereditary because it occurs in several members of one family is not necessarily correct. The transmission is not according to the Mendelian law. It may be more accurate to consider the progeny pathology due to some abnormality of the parent. If studied from this point of view, new aspects appear possible. That there can be an alteration in sex development artificially produced has been shown by Greene and Ivy,[9] who injected both estrone and testerone into pregnant female rats and produced changes in the offspring. They state that the female progeny showed hypospadias with estrone and

varying degrees of heterosexuality with testerone. The changes persisted; apparently the alteration was irreversible.

Is it possible then that a mother may have an unbalance in secretion which results in irreversible pathology in the progeny or that an abnormal placental transmission may exist which leads to the same results? Benner suggested that neutralization of maternal hormones may be a function of some "x" substance from the adrenal cortex. If some such pathology is present, the absence of cortical hormone or the cells producing this may be embryological and not due to atrophy from overgrowth of another cell.

The sex differences in the cases are striking. Grollman listed only twenty-four cases of the juvenile form of adrenogenital syndrome, and of these nineteen were in girls and five in boys. Of the five in boys, all were due to tumors other than bilateral hypertrophy of the adrenals.

He stated that Gallais recorded eleven cases of pseudohermaphroditism with adrenal pathology in females. About 15 per cent of the female and only 0.7 per cent of the male pseudohermaphrodites are due to adrenal hypertrophy. The adrenal pathology should produce in the male macrogenitosomia, but Young stated this is an exceedingly rare occurrence and of the cases he listed with macrogenitosomia not one is due to cortical hypertrophy of the adrenals. Wilkins and his associates stated that their case is the first in which at autopsy diffuse bilateral hypertrophy of the androgenic tissue has been found in the male. They cited two cases in the literature that were suggestive of the same syndrome, but not proved by autopsy or operation. Our patient, Wilkins', Butler's, and two of Dijkhuizen and Behr's patients were males. If the female pseudohermophrodites due to adrenal cortical hypertrophy belong etiologically in this group, the suggestion is inescapable that hypertrophy of the androgenic zone is accompanied by absence of the interrenal tissue more frequently in the male than in the female. Such a deficiency would lead to an early fatal outcome before the macrogenitosomia became apparent; consequently cases would usually die unrecognized.

INCIDENCE

Even if cases in infancy have been missed, the disease is not common. Potter and Adair[10] do not mention hypertrophied adrenals in their book on fetal and neonatal deaths. Once a syndrome is recognized, however, the incidence often apparently increases. Other peculiar familial diseases better known, such as erythyroblastosis fetalis and familial steatorrhea, are not common, and the cases of cortical insufficiency with adrenogenital syndrome may have a similar frequency.

TREATMENT

Experiments on animals and the findings in the few cases reported suggest certain lines of therapy to be followed. When adrenalectomy

is performed on dogs, destruction may be complete necessitating total replacement by cortical hormone therapy. In others it is incomplete, and the animal may be carried for varying periods of time on excess salt intake. Grollman has pointed out that salt therapy is not substitution therapy and animals so carried eventually die suffering from kidney and liver damage. Wilkins' case showed evidence of kidney damage. Some animals have remnants of adrenal tissue left that may hypertrophy and supply the animal with adequate hormone after being carried temporarily with salt or cortical hormone.

From this knowledge, therapy should proceed. The acute case in or near collapse should receive salt subcutaneously, intravenously, or both, and glucose solution may be given intravenously with normal saline. Sodium bicarbonate may be given advantageously with the saline in the ratio of 2 parts of salt to 1 part of sodium bicarbonate. Percortin should be administered hypodermically. After chemical balance has been established, treatment should be regulated to meet the need of the individual patient. If a moderate intake of salt will suffice to carry him, it may not be necessary in some instances to use hormone or desoxycorticosterone acetate. With the drug available for sublingual administration, dosage may be varied from day to day while the patient is watched. When the desoxycorticosterone acetate is given, salt should be moderately restricted or there may be retention of fluid in the tissues and synovial cavities. A normal amount of potassium should be maintained in the food.

Whether or not there is a surgical approach to the relief of androgenic overproduction in these cases is doubtful. Young has performed bilateral operation for removal of adrenal cortex on female pseudohermaphrodites with fairly good results. But with adrenocortical insufficiency as a complicating factor the risk is great, and there is no reason to believe that the insufficiency would be benefited by partial removal of the androgenic tissue. There is no evidence that this bilateral hypertrophy tends to become malignant; pseudohermaphrodites with androgenic hypertrophy have lived to a mature life without degeneration of the tissue.

X-ray therapy to decrease the amount of functioning androgenic tissue may be worth a trial.

Whether or not the use of other hormones to produce compensatory atrophy may eventually offer another type of therapy is problematical. Our knowledge about the antagonism of hormones is still meager.

PROGNOSIS

The ultimate prognosis of the cases carried from infancy on hormones or desoxycorticosterone acetate is not known. The case reports of Wilder[11] prompted us to get an early electrocardiogram on this patient. The picture is reproduced here. It may indicate some pa-

thology. It is hoped that this child may be followed not only with repeated electrocardiograms but also with blood chemistry analysis from time to time for evidence of kidney and liver damage.

SUMMARY

This review of a relatively new syndrome represented by adrenal cortical insufficiency associated with the adrenogenital syndrome is presented with the hope that it will focus attention on the condition and lead to further studies on the pathology, etiology, and treatment.

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PERIARTERITIS NODOSA IN A NINE-YEAR-OLD CHILD

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PERIARTERITIS nodosa is a rare disease first described by Kussmal and Maier in 1866.[1] Because of its polymorphic character, an intravitam diagnosis is a rarity. Two hundred and thirty cases were reported in the literature up to 1937.[2] Most of the cases appeared in adults, only thirty-two, or 13.9 per cent, having been reported in children. This case report is of interest because it describes the disease in a child whose outstanding sign and symptoms were referable to the heart.

Though an infrequent disease, periarteritis nodosa is widespread, cases having been reported in persons of Great Britain, France, Scandinavia, Argentina, and the United States.[1] Cases have also been reported in the deer, pig, calf, and dog.[3]

The specific cause of the disease still remains unknown, though several theories have been entertained. Syphilis, some infectious agent, rheumatic state,[4] and allergy[5] have all been considered as etiological factors.

In general, there are two schools of thought. The febrile course, polyneuritis, and cardiac involvement, tend to make some investigators favor an unknown infectious agent as the etiological factor. The degenerative lesions found anatomically cause other investigators to feel that the disease is a response to a chronic debilitating illness.

Though rare, periarteritis nodosa is an important disease because of its fatal termination. Of all reported cases, 95 per cent ended in death; 70 per cent of these patients died within four months of onset.[6] This acute form of the disease is the one noted in children.

Symptoms vary according to the arteriolar group involved. Thus meningeal,[1, 9] cardiac, abdominal, neuromuscular, and dermatological[7, 8] syndromes have been reported. Despite the fact that cardiac involvement is found in 70 per cent of the autopsies, clinically, symptoms and signs referable to the heart are uncommon.

Anatomically the lesions need not be nodose but may extend over large segments of the affected arteries.[9] The primary lesions are in the small arteries and arterioles, not in the larger elastic arteries and veins.[10] The general pattern is that of an acute inflammation of the vessel wall, loss of muscle followed by repair and proliferation. A fibrinous exudate invades all layers of the arterial wall; this is soon followed by a dense cellular infiltration with lymphocytes, plasma cells, and eosinophiles. Thrombosis and aneurysms appear as a result of injury to the coats of the involved vessels.

From The Pediatric Service of the Queens General Hospital, Jamaica, N. Y.; Dr. H. A. Reisman, Director.

CASE REPORT

J. T., a male white child, was first observed in the outpatient department of the Queens General Hospital. On May 17, 1939, the patient appeared at the clinic because of frequent intermittent nonseasonal attacks of asthma. One month later the child was re-examined for complaints of joint pain, low-grade fever, anorexia, and swollen cervical glands. A blood count at this time showed 14,600 white blood cells and an eosinophilic count of 40 per cent. One month later (June 21, 1939) the child was admitted to the Pediatric Service because of irritability, loss of weight, joint pains, low-grade fever, and swollen glands.

Family history revealed a paternal aunt suffering from asthma.

Past history revealed that the patient had been subject to an attack of measles, whooping cough, and pneumonia. An allergic investigation, at another institution, was unfruitful, though at that time a white count of 9,150 with 12 per cent eosinophiles was observed.

Physical examination revealed a 9-year-old, pale, white, male child, appearing chronically ill. Only two positive findings were elicited at this initial examination; they were enlarged cervical lymph nodes and an enlarged heart. The point of maximal intensity was in the fifth space 2.5 cm. lateral to the midclavicular line.

The patient was under observation for a period of four months from May 17, 1939, to September 16, the day of his death. During his stay in the hospital his many signs and symptoms gave rise to a number of diagnoses. The persistent elevated eosinophilic count indicated a possible allergic factor. The enlarged heart, the rapidly progressing edema, and the quick response to digitalis and oxygen therapy pointed to unknown or rheumatic heart disease with decompensation. On the other hand, the massive accumulation of fluids and cardiac signs raised the question of Pick's disease (adhesive pericarditis) and polyserositis. Lack of conformity to a definite clinical picture, eosinophilia, and the general appearance of the patient brought up the question of trichinosis and possibly periarteritis nodosa. Many exclusion laboratory tests which are listed in the accompanying data were done to rule out acute bacterial infection and worm infestation. Credit must be given to the resident staff for their diligence and persistent effort to establish a diagnosis. Pertinent facts during the course of the patient's stay in the hospital are as follows:

1. Fever was low-grade, 99° to 102° F. (rectal).
2. Pulse was variable, 104 to 136.
3. Respirations were rapid, 24 to 40.
4. About two weeks after admission (July 6, 1939) the patient began to show signs of gradual cardiac decompensation. A puffy face, increasing dyspnea, orthopnea, elevated pulse rate, gallop rhythm, râles in the left chest, and slowly advancing general edema with hepatomegaly all gave evidence of a failing heart. From July 26 to Aug. 2, 1939, inclusive, 1,700 c.c. of fluid were removed by thoracentesis. At various times a systolic murmur with lateral transmission and an intermittent friction rub were heard in the apical area.
5. Manifestation of acute infection rapidly subsided during the patient's stay in the hospital. There were no further complaints of joint pains, and at no time could one find a swollen, hot, red joint. No attacks of asthma were observed while the patient was in the ward.

TABLE I

DATES	6/21/39	6/28/39	7/26/39	8/9/39	8/22/39	9/12/39
Hbg.	74%	54%	80%	104%	117%	86%
R.B.C.		3.32M	3.79	5.2	5.2	4.53
W.B.C.	16,000		7,560	8,600	11,900	13,850
Polymorphonuclear cells	26%	40%	44%	59%	31%	51%
Eosinophiles	39%	29%	2%	3%	41%	21%

Lymphocytes showed a relatively normal picture.

Weight.—He weighed 50 pounds on admission and 46 pounds four days prior to exitus. The weight rose to 62 pounds during the period of massive edema.

Laboratory, X-Ray, and Exclusion Tests.—From June 21, 1939, to the day of death the blood pictures showed the variations given in Table I.

X-Ray.—On June 22 the lung field showed evidence of congestion and the heart showed an enormous enlargement to the right and left, with the upper cardiac border especially prominent, suggesting mitral valve pathology.

As the patient developed the massive edema, the chest pictures corroborated the clinical findings, so that on August 1 opacity of the entire right lung field with considerable displacement of the heart to the left was noted. The heart was still enlarged. By August 28 the lungs were clear, though the heart was still considerably enlarged, having a transverse diameter of 15.5 cm. against a measurement of 20 cm. for the diameter of the thoracic cage. The gastrointestinal series was normal.

Electrocardiogram.—Eight tracings taken during the patient's stay in the hospital showed a variable axis deviation and normal P-R and QSR intervals. Some tracings showed a slurred P, a prominent Q_3, an inverted T_3, and an elevated ST_3.

Exclusion Tests.—The blood culture and Wassermann tests were negative. Nose and throat cultures, Mantoux, as well as a search for the tubercle bacillus, in the gastric contents were all negative. Examinations of sputum and gastric contents were negative for actinomycosis. Agglutination tests for echinococcus infestation as well as examinations of blood smears for malaria were also negative. Blood agglutination for the typhoid-paratyphoid group yielded a negative result in series of 1:20 to 1:320.

Blood Chemistry.—Sugar was 75 mg. per cent; urea, 12.2 mg. per cent; creatinin, 1.2 mg. per cent; cholesterol, 125 mg. per cent; chlorides, 553 mg. per cent; the albumin-globulin ratio, 3.6 to 2.4. The above taken at various times showed very little variation.

Miscellaneous.—P.S.P. was 42 per cent on Aug. 31, 1940, although the urinary findings were normal. The icteric index was 5; venous pressure, 140 mm.; glucose tolerance, 52, 95, 98, 91. Sternal puncture showed eosinophilic leucocytes.

Treatment was symptomatic. Digitalization, oxygen tent, and the mercurials caused a remarkable change for the better. One month after the onset of cardiac decompensation (Aug. 7, 1939) the patient showed a complete disappearance of the signs of failure. The liver receded; respiration and pulse decreased; and the pleural and ascitic fluid became markedly diminished. Three and a half weeks later the patient complained of abdominal pains and vomiting. By September 14 there was an improvement in the patient's condition. The abdominal pains disappeared, and the appetite was increased. On September 16, the fourth month of the patient's sojourn in the hospital, while being prepared for a muscle biopsy to establish a diagnosis, the patient died.

As noted previously, the deciding factor in the diagnosis of periarteritis nodosa is an autopsy. A post-mortem examination was made.

Anatomically, there was a generalized necrotizing periarteritis and arteriolitis involving the heart, lungs, and liver to a great extent. The kidneys, muscles, intestines, spleen, lymph nodes, and adrenals showed minimal to moderate pathologic changes.

When the pericardial sac was opened, numerous friable adhesions between the visceral and parietal layers were noted. A thick layer of hemorrhagic and fibrinous material covered the visceral pericardium. The heart itself was markedly enlarged to the left and right. The auricular chambers appeared normal in size and thickness. The right ventricle was markedly hypertrophied, measuring 8 mm. in thickness, and had a slightly dilated cavity, as well as a prominent pulmonary conus. The left venticle measured 18 mm. in thickness, and the cavity was markedly dilated. Scattered throughout both ventricular walls and the interventricular septum and papillary muscles there were minute areas of hemorrhage intermingled with streaky

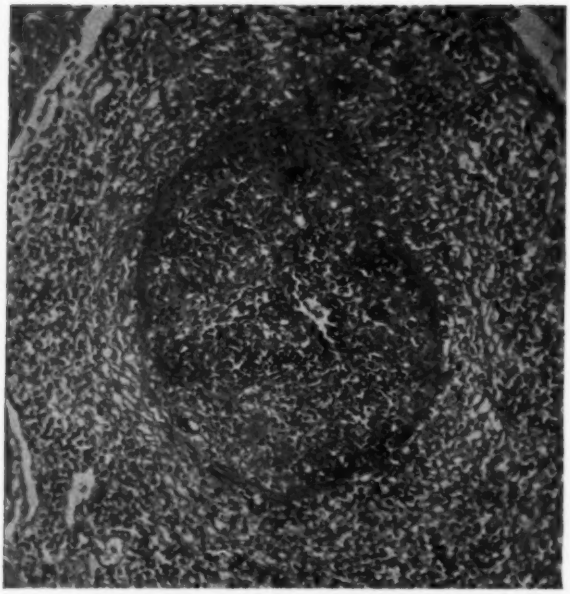

Fig. 1.—Coronary artery (×100). Marked necrotizing arteritis and periarteritis with narrowing of lumen.

Fig. 2.—Pulmonary arteries (×100). Focal necrotizing arteritis and periarteritis with surrounding reactive changes.

yellowish areas. The valves revealed no gross abnormality. The coronary vessels appeared slightly thickened. The aorta was elastic and showed a minimal degree of lipoid change in the supravalvular portion.

The lungs were found free in the pleural cavities and were pink in color. In the right lung, at the base of the lower lobe, there was a firm nodular area, which on cut section revealed a rough, quadrangular, reddish-brown area, extending into the parenchyma, and measured about 3 cm. in diameter. A thin zone of surrounding recent hemorrhage was noted. Section of the tissue above this area revealed an old greyish thrombus in a vessel which was completely occluded. Small nodular areas were distributed throughout the right lower and upper lobes. Scattered throughout both lungs minute, yellowish, nodular foci could be made out, which on closer inspection, seemed to contain a central channel.

The heart on multiple sections showed extensive recent necrosis of muscle, with marked eosinophilic inflammatory reactions; old healed fibrosis was especially noted in the papillary muscles. Marked necrotizing arteriolitis with thrombosis and perivascular inflammation, cell reaction, as well as recanalized thrombi were also seen.

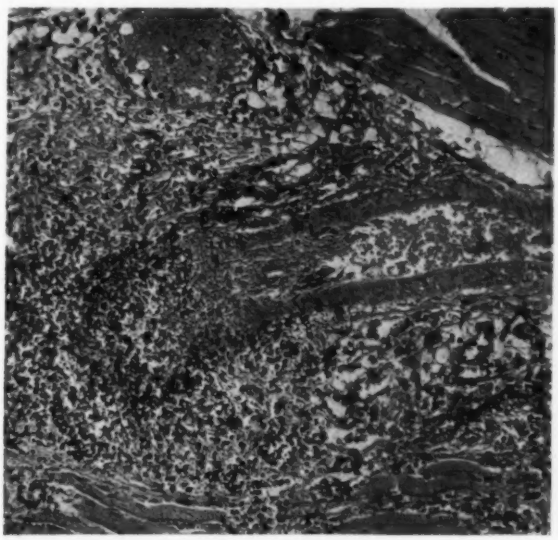

Fig. 3.—Diaphragmatic artery (×100). Marked focal necrotizing arteritis and periarteritis.

Microscopic examination revealed many interesting findings. The diaphragm showed an arteriole with one portion necrotic, surrounded by an intense inflammatory reaction which included the presence of many eosinophiles and much necrotic muscle.

Arterioles in the lungs showed a similar picture. The liver showed an involvement of the arterioles in the portal areas with recanalized old thrombi, as well as acute changes.

The mediastinal lymph nodes and intestines showed similar sizable arteriolar changes. The capsules of the adrenals showed a marked involvement of the arterioles with recanalization of the thrombus.

The brain revealed an old subarachnoid hemorrhage, with thickening of the membrane and old blood pigment.

Anatomic diagnosis follows:

1. Generalized necrotizing panarteritis and arteriolitis with involvement of
   a. Heart—marked
   b. Lungs—marked
   c. Liver—marked
   d. Kidney—minimal
   e. muscle—minimal
   f. Gut—minimal
   g. Spleen—minimal
   h. Lymph nodes—minimal
   i. Adrenal—moderate.
2. Hypertrophy and dilatation of left ventricle.
3. Hypertrophy and dilatation of right ventricle.
4. Extensive necrosis and hemorrhage of myocardium and papillary muscles.
5. Hemorrhage and fibrinopurulent pericarditis with effusion.
6. Chronic passive congestion of lungs, marked.
7. Old thrombus in pulmonary artery in right lower lobe.
8. Infarct of right lower lobe, recent.
9. Chronic passive congestion of liver.
10. Acute mediastinal lymphadenitis.
11. Acute splenitis.
12. Old subarachnoid hemorrhage, temporal lobe.

SUMMARY

A case of periarteritis nodosa is reported in a child 9 years of age. This patient fell into the cardiac group of the disease, for signs of cardiac insufficiency were noted throughout his course. At autopsy, the microscopic and gross findings were those of periarteritis nodosa.

Acknowledgment is hereby made of the kind cooperation of the Department of Pathology, Dr. Angrist, Director.

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ACUTE INTERSTITIAL MYOCARDITIS IN AN INFANT

Report of a Case With Autopsy Findings

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History.—H. T., a 1-year-old white girl, was admitted to the Jewish Hospital Pediatric Service on March 31, 1935, with the complaint of rapid breathing with grunting expiration, which had begun ten days previously and had become progressively worse. Her appetite failed, and she lost 5 pounds. For the previous two days she had been irritable and drowsy.

Birth and developmental history were normal. The child had begun to walk two weeks before the onset of this illness. There had been no previous illnesses of note. The child had played with toys, the paint on which which was found to contain lead.

Family History.—Both maternal grandparents had arteriosclerotic heart disease.

Physical Examination.—Examination showed a well-developed and nourished child, irritable, but alert. The temperature was 99° (rectal); pulse, 160; respirations, 60. There was a mucoid nasal discharge. Breathing was almost entirely diaphragmatic, with grunting expiration. The percussion note was resonant, and the breath sounds were normal. No râles were heard. The heart was not enlarged. The sounds were of good quality. A systolic murmur was heard best over the mitral area and was transmitted into the left axilla. The murmur was less intense over the aortic area. The liver could be felt 1 cm. below the costal margin in the midclavicular line. The spleen was not palpable. The child assumed a gun-hammer position. The patellar reflexes were hyperactive. The biceps and abdominal reflexes were not elicited. Babinski's, Kernig's, and Brudzinski's signs were negative.

Laboratory Data.—On admission acetone and a trace of albumen were present in the urine, but these disappeared during the hospital stay. Dr. Robert Kehoe reported no increase of lead in the urine.

Repeated counts showed a red blood count of about 3,500,000, with hemoglobin 60 to 65 per cent. The white blood counts varied between 14,000 on admission to 10,000 later on, with the differential count showing 47.5 per cent polymorphonuclears and 48 per cent lymphocytes. There were moderate anisocytosis, slight poikilocytosis, and on one occasion 1 per cent eosinophiles and 2.5 per cent reticulocytes. There was no stippling. Blood calcium was 11.2 per cent.

The lead content of the stool, determined by Dr. Kehoe, was normal.

Spinal fluid pressure was normal. Globulin in the spinal fluid was negative. There were four cells per cubic millimeter. Lead content was at the upper level of normal. Sugar was 86 mg. per cent. The Wassermann test was negative.

The Schick test was negative. Tuberculin tests with P.P.D. No. 2 were negative. Cultures from nose and throat showed staphylococci. No Klebs-Löffler organisms were found. The mother's blood Wassermann test was negative.

Roentgen Examinations.—On April 1, 1935, the ulna and radius showed no lead line. On April 2, 1935, lung films were interpreted as follows: Both lungs showed diffuse parenchymatous infiltration along the bronchial tree, apparently due to a bronchitis. The heart was normal in position, size, and shape.

Teleoroentgenograms of the chest on April 11, 1935, showed the same findings as above.

On April 23, 1935, the heart was deviated to the right, and in addition to the previous findings, there was a triangular dense shadow at the base of the right lung, possibly produced by atelectasis of the right lower lobe.

From the Pediatric Service of the Jewish Hospital, Cincinnati.

Electrocardiogram (April 27, 1935).—The electrocardiogram showed normal sinus rhythm and a rate of 165 per minute. In Lead I, P wave was upright; PR interval, 0.14 second; R wave main deflection; RST segment isoelectric; T wave inverted. In Lead II, P wave was upright; PR interval, 0.16 second; R wave main deflection; RST segment isoelectric; T wave inverted. In Lead III, P wave was upright; PR interval, 0.16 second; R wave main deflection; RST segment isoelectric; T wave absent.

The impression was sinus tachycardia. In view of the T wave changes in all three leads, this record is indicative of the presence of myocardial damage.

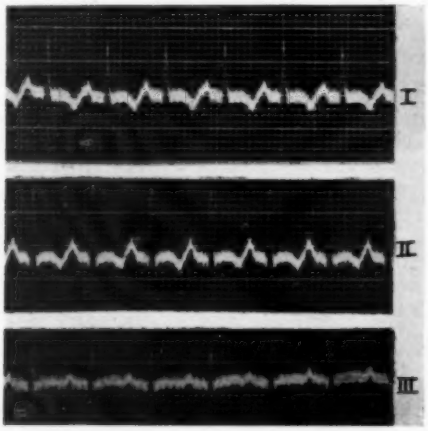

Fig. 1.—Electrocardiogram taken April 27, 1935, shows a normal sinus rhythm. Rate, 165 per minute. The T waves are inverted in Leads I and II and absent in Lead III; this indicates the presence of myocardial damage.

Course in the Hospital.—The pulse and respiration remained rapid throughout the child's illness. The pulse rate varied but was never below 130. As a rule, it was found to be between 140 and 180, averaging about 155 per minute. The respiratory rate varied between 30 and 80, averaging about 60 per minute. The child was fever-free for the most part, except for slight rises on several occasions, at which times she had nasal congestion with mucopurulent nasal discharge and some cough. The liver gradually increased in size, until it reached within two fingerbreadths of the umbilicus, and the spleen likewise increased in size until it could be felt one fingerbreadth below the costal margin. The expiratory grunt became less marked at first but soon returned to its original intensity. Gradually the lips became cyanotic; a persistent cough developed; and on April 27 breath sounds and percussion note became impaired at the right base. Quinine had no effect on the heart rate, and the child continued to grow worse. On May 1, 1935, because of the possibility of the presence of a nonopaque foreign body, bronchoscopy was performed under local anesthesia. Nothing abnormal was found. The child died May 2, 1935, thirty-three days after admission and forty-three days after onset of the symptoms, with a terminal bronchopneumonia.

Treatment was chiefly symptomatic. No cardiac drugs were used.

Necropsy Findings.—Necropsy was performed eight hours post mortem by Dr. Sander Cohen, from whose report the following excerpts are presented. The child was well developed and nourished. The pericardial sac was moderately distended and contained about 75 c.c. of clear, yellowish fluid. The heart was enlarged, but externally did not appear remarkable. All the valves and valve orifices appeared

normal. There were no auricular thrombi. There was no evidence of a patent foramen ovale, patent interventricular septum, pulmonary stenosis, or patent ductus arteriosus. Both the aorta and pulmonary arteries arose normally from their respective ventricles. Both ventricles were dilated, and there was definite cupping with flattening of the columnae carneae. The intima of the pulmonary artery and aorta appeared normal. The heart muscle on section showed no abnormal changes except for edema.

The right pleural cavity contained about 250 c.c. of clear, straw-colored fluid; the left, about 150 c.c. There was no evidence of pleuritis.

The right lung presented numerous patchy firm areas. On section, these had a dark red color and a granular appearance, and stood up slightly above the level of the surrounding tissue. Similar, though fewer, areas were found in the left lower lobe. There was no evidence of obstruction of any bronchus. The hilar glands were enlarged, reddened, and swollen, but there was no evidence of obstruction from this source. The liver was enlarged, extending 6 cm. below the xiphoid. The liver tissue was somewhat pale but of good consistency.

The suprarenals were of usual size, but on section showed practically no medulla.

In the ileum and colon the lymphoid tissue was found to be greatly swollen, with abnormal prominence of Peyer's patches and of the solitary follicles. The mesenteric nodes were all somewhat enlarged and on section presented grayish, smooth surfaces.

The thyroid, thymus, kidneys, stomach, duodenum, and bladder were not remarkable.

The brain showed moderate congestion, edema, and a moderate amount of fluid in the subarachnoid space. Multiple sections through the brain and cervical spinal cord showed no evidence of inflammatory or degenerative processes.

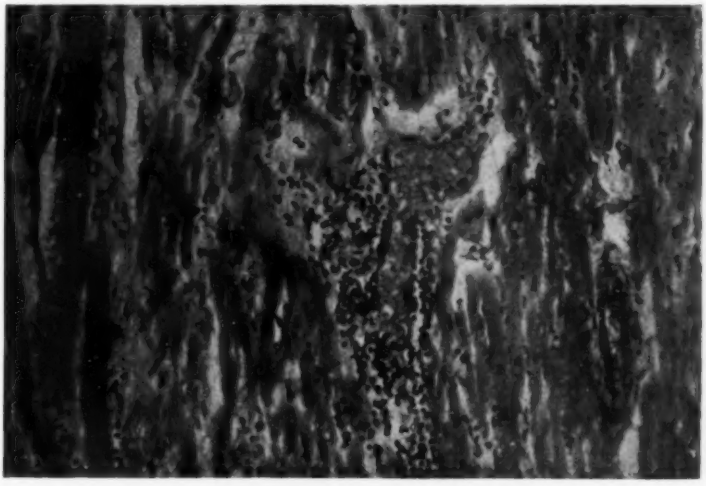

Fig. 2.—Focal subacute myocarditis; myocardial edema and fibrosis.

Microscopic Findings.—On microscopic examination, the heart showed toxic myocarditis, with myocardial edema and marked congestion, focal subacute myocarditis, with perivascular fibrosis. The lungs showed extensive lobular pneumonia, the chief reaction cells being endothelial leucocytes and lymphocytes. No areas of caseation or vascular changes were seen. Occasional "heart failure" cells were seen

in the alveoli. Some of the mononuclear cells were multinucleated. Special stains of these sections failed to reveal acid-fast organisms. The hilar nodes showed subacute lymphadenitis. There was hypoplasia of the medulla of the suprarenals. The brain cortex, basal ganglia, pons, medulla, and cervical cord showed edema. There was no evidence of encephalitis. The small bowel showed lymphoid hyperplasia, and the large bowel, marked congestion with hemorrhage into the mucosa. There was chronic passive congestion of the liver, with toxic changes in the liver, kidneys, and thymus. The pituitary and the other organs were not remarkable.

Because of the interest created by this case and the insufficient findings at autopsy to explain the clinical picture, sections of the heart and lungs were sent to four prominent pathologists for their interpretations. The following replies were received.

REPORT 1.—"The heart muscle shows slight focal infiltration, with few leucocytes and mononuclear cells. The most striking changes are found in the lung, and these consist of the alveoli being filled with large mononuclear cells which very frequently contain vacuoles, apparently fat.

"I take it for granted there was no tuberculosis in this case, because your gross description does not mention any changes. Otherwise, one would possibly think of a gelatinous pneumonia.

"I do not believe that the lesions found in any way account for the clinical symptoms, but I believe that they are secondary terminal events.

"The lesion in the heart muscle suggests a toxic etiology."

REPORT 2.—"It is certain that the heart plays the most important role. Both sections show a very marked, diffuse, not very recent myocarditis, with infiltrates of leukocytes and lymphocytes, and partly also fibroblasts and macrophages. These infiltrates are located partly along the smaller vascular branches and partly between the muscle fibers. Besides this, there is a certain degree of edema which makes a little bit unusual picture of the whole change. The muscle fibers, especially on one slide, show central whitish empty spaces and are almost completely dissolved. Possibly some glycogen deposits were involved within these degenerating fibers. This lytic type of muscle fiber degeneration is not very common.

"The lungs show only secondary changes due to chronic passive hyperemia. There is very marked dilatation of all the capillaries which are engorged with erythrocytes. The alveoli contain edema fluid and a large number of macrophages which contain hemosiderin granules (heart failure cells). The same content is present in the bronchioles and even in the larger bronchi. Some areas show atelectasis, probably brought about by respiration of air during the occlusion of the respective bronchi by edema fluid. The interstitial tissue of the lung is partly hypertrophied as a first sign of congestive fibrosis and shows some smaller hemorrhages as a result of congestion.

"Summarizing, I should say: Chronic diffuse myocarditis without any suspicion of a rheumatic disease, more closely resembling some cases of myocarditis following diphtheria. (Perhaps a very superficial diphtheria of the nose some months ago did not lead to any medical treatment.)

"The heart, at least for weeks, was in a stage of decompensation as the chronic passive congestion of the lungs indicates. I can hardly give a convincing explanation for the grunting respiration which was so remarkable during life, but I think it was in connection with atelectasis and edematous occlusion of the smaller bronchi."

REPORT 3.—"The slides . . . present a very definite problem in diagnosis which I do not feel I have surmounted. The sections from the heart certainly show evidence of a chronic inflammatory process. There is a definite interstitial edema associated with some connective tissue proliferation and accompanied by areas of cellular infiltration, chiefly perivascular in distribution. These cells appear to be chiefly plasma

cells, lymphocytes, and large mononuclear leukocytes. There is a curious fraying out of the muscle fibers which one sees not infrequently in children in congestive heart failure.

"The sections from the lungs are similarly suggestive of congestive heart failure, with considerable pigmentation. There are a number of distinct lesions, some of which do not seem to bear any particular relationship to each other. In the first place, there is an obvious atelectasis which strikes me as probably being largely congenital in origin. There is, likewise, a definite inflammatory pneumonitis with a very extensive mononuclear cellular reaction both within the alveolar walls and an exudate in the lung alveoli. There is a similar peribronchial mononuclear increase. These changes suggest a chronic lung infection.

"The vascular changes do not seem to be adequate to make one more than suspect a syphilitic background, but the cardiac picture is almost identical with that so frequently described by Warthin as a feature of congenital syphilis. . . . I do not see anything which arouses in my mind the likelihood of tuberculosis.

"All the members of the staff have been over these slides with great interest and are inclined to concur in these few general comments which I am offering."

REPORT 4.—"My best guess is that the changes in the myocardium are toxic in nature and that diphtheria certainly is a possibility. The most important changes in the lungs are, in my opinion, secondary to failure of the heart. I could find no evidence of either tuberculosis or syphilis."

COMMENT

This is an example of that rare form of heart disease known as acute interstitial myocarditis, also known as acute isolated myocarditis, the first clear description of which was given by Fiedler[1] in 1890, although Steffen's[2] two cases, reported in 1888, were probably the same condition. The clinical picture is one of progressive myocardial failure unassociated with the usual causes of myocardial damage. The myocardium alone is diseased, while the pericardium, endocardium, and heart valves are not affected. Histologically, the inflammatory changes are found chiefly in the interstitial tissues, although in some cases the parenchyma is also involved.

Scott and Saphir,[3] in 1929, were able to gather thirty-six cases with autopsy findings, mostly from the foreign literature, to which they added two of their own. In the majority of these there were no antecedent infections which might have been suspected of causing the myocarditis. The youngest patient in this series was 3 years of age.

Maslow and Lederer[4] reported a case in a 19-month-old child, Lindberg,[5] in an 11-month-old child; Kenny and Sanes[6] reported two cases in infants which they called parenchymatous myocarditis. One patient, a girl 1 year of age, had had bronchopneumonia six weeks before the onset. She had been well for two weeks; then dyspnea and cyanosis were noted; and she died in ten days. The other case was in a boy 6 months of age. The only preceding illness was stomatitis of three days' duration some months before. He became dyspneic and cyanotic and died in a few hours.

According to Helwig and Wilhelmy,[7] acute interstitial myocarditis occurs most frequently in persons between the ages of 20 and 50.

The diagnosis of acute interstitial myocarditis is very difficult. According to Maslow and Lederer,[4] who reviewed the literature up to 1933, diagnosis before death had never been made.

The etiology is obscure. Microscopic sections of the heart and lungs, together with a complete history of our case, were sent to four nationally known pathologists. They all found myocarditis and terminal pneumonia, but they did not agree as to the cause. One strongly suspected congenital syphilis; one was sure it was not syphilis; and the other two did not commit themselves on this point. There was no evidence of syphilis in our case either serologically or on physical examination, nor was there any known antecedent illness which might have caused the myocarditis.

Acute interstitial myocarditis should be considered in cases of prolonged tachycardia in infants and children in whom no other cause can be found.

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ACTINOMYCOSIS TREATED WITH SULFANILAMIDE

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THE etiology and pathology of actinomycosis have been understood for some time. However, it is generally agreed that in the past the treatment has been quite unsatisfactory. Many different forms of treatment have been tried.[1, 2] A few of these are: (1) radical surgery, drainage and curettement; (2) roentgenotherapy; (3) iodides; (4) copper sulphate; (5) colloidal gold; (6) insulin and intravenous glucose in an attempt to elevate the basal metabolic rate; (7) autogenous vaccine; (8) nonspecific protein therapy; and (9) thymol by mouth and locally. More recently reports of treatment with sulfanilamide and sulfapyridine have appeared.

Walker[3] reported a case of actinomycosis following the removal of a gangrenous appendix in a 23-year-old patient. Treatment with potassium iodide was of no benefit, but a complete cure was obtained with sulfanilamide. Miller and Fell[4] reported a case of abdominal actinomycosis in an 11-year-old boy. Treatment with thymol, potassium iodide, and x-ray was a failure. He was given sulfanilamide, and improvement was noted within one week. After several months he was completely well. Sudler and Johnson[5] reported two cases of actinomycosis of the cervicofacial type. Both patients were cured after sulfanilamide therapy. Hall[6] reported a case of pelvic actinomycosis in a 20-year-old woman. She was apparently cured by sulfanilamide after potassium iodide had been of no avail. Mac Charles and Kippen[7] reported three cases of cervicofacial actinomycosis, two in adults and one in a 9-year-old girl. Good results were obtained with sulfanilamide supplementing surgical drainage. Ogilvie[8] reported a case of abdominal actinomycosis with recovery after treatment with sulfapyridine. He made the suggestion that the drug may have eliminated the secondarily infecting streptococcus, allowing the patient to effect her own cure. Morton[9] reported three cases; two of the patients were treated with sulfanilamide. A 46-year-old man had the cervicofacial type, and the process had progressed up to the base of the skull by direct extension, causing a meningitis. Treatment consisted of surgery, sulfanilamide, potassium iodide, blood transfusions, and vaccine, but the patient died. The second patient in whom sulfanilamide was used was a 34-year-old man. The disease involved the breast and axilla. At the time of the report the man was improved but not well. Dorling and Eckhoff[10] reported five cases of abdominal actinomycosis treated with sulfanilamide, sulfapyridine, or both. All the patients had severe infections; four recovered completely, but one died. The latter case in an 18-year-old boy was one of a rapidly spreading peritonitis of appendicular origin.

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Sulfanilamide was thought to result in some improvement, but the patient developed a pelvic abscess and continued peritoneal infection. Clemens[11] reported a case of abdominal actinomycosis in a 10-year-old boy. The child failed to respond to sulfanilamide in adequate dosage over a period of twenty-eight days, but recovery occurred under thymol therapy. Dobson, Holman, and Cutting[12] reported three cases; one was in a 65-year-old man with actinomycosis of the jaw, another in a 24-year-old man with involvement of the lung and rib cage, and a third in a 12-year-old boy with extensive abdominal actinomycosis. Therapy included the use of sulfanilamide, iodides, and x-ray. Sulfanilamide was considered by the authors to have been of definite value in determining the favorable outcome of these cases.

CASE REPORT

First Hospital Admission.—An 11-year-old white girl was admitted on April 4, 1939, and discharged on July 6, 1939. She had developed redness, swelling, and tenderness on the dorsum of her right foot three months before admission. Two weeks previously she had dropped a chair on this foot. A short time later draining sinuses developed on the dorsum and medial aspect of the foot. About one month after the lesion on the foot appeared, several sinuses developed from a similar lesion on the front of the chest. A bloody purulent discharge drained from these openings. About two weeks later a similar lesion appeared over the right hip and drained spontaneously from several openings. About the same time there developed a soft tender swollen area on the right cheek. The girl had had a little fever. She had had no cough; her appetite had been good; she had lost considerable weight. There was nothing remarkable in the past history and family history except that a grandfather was said to have had tuberculosis.

Physical Examination.—Temperature was 99° F.; pulse, 120; respiration rate, 28; blood pressure, 90/60; weight, 51 pounds. The patient appeared chronically ill and emaciated but was in no apparent discomfort. The cervical and inguinal lymph nodes were somewhat enlarged. On the dorsum of the right foot was a thickly crusted area; around this area was slight redness and swelling of the soft tissue. Passive motion caused slight pain. In the region of the right hip there were three deep, round, draining sinuses, each being about 0.25 inch in diameter. There was no limitation of motion of the right hip joint. Over the upper portion of the sternum was a bluish-red discolored area from which there were several sinuses draining a thin yellowish fluid. The upper part of the lesion was covered with a thick, firm crust. Just medial to the right nipple there were two swollen red, conical shaped, soft, very tender areas. On the right cheek there was a thin-walled, yellowish, fluctuant, nondraining area which was tender but did not appear to involve the deeper structures. The mucous membranes of the mouth were pale; the teeth were dirty; the tonsils were not enlarged; the chest was symmetrical. At the right apex and in the axillary region there were impaired resonance and suppression of breath sounds. On examination of the heart the point of maximal impulse was felt in the sixth interspace at the nipple line. There was a soft systolic murmur at the apex.

Laboratory Data.—Urine was normal; blood determination showed 4,420,000 red blood cells, 10.6 Gm. hemoglobin, and 19,000 white blood cells. Differential count indicated 90 per cent polymorphonuclear neutrophiles, 1 per cent eosinophiles, 9 per cent lymphocytes. Kahn test was negative. Stools were negative for parasites. Tuberculin tests from 0.00001 mg. to 0.1 mg. were negative.

On the eighth hospital day a biopsy was taken from the lesion on the right hip. Microscopic sections revealed an area of typical sulfur granules. Also, *Actinomyces bovis* was found in fresh preparations in the pus obtained from one of the lesions on the chest.

X-ray Findings on Admission.—"There is a heavy infiltration in the region of the right hilus with extension into the lung fields, but the extreme periphery of the lung field appears clear. Left lung shows no significant change. The first metatarsal of the right foot shows a low-grade osteomyelitis, probably of long standing. There is a marked disuse atrophy of all the bones of the foot." The right hip showed no change other than the generalized disuse atrophy. No pathologic change was seen in the sternum.

Fig. 1.—Photograph of patient on April 15, 1939, at beginning of sulfanilamide therapy.

Course in Hospital.—The patient was given one blood transfusion of 200 c.c. on April 14, 1939. On this same date sulfanilamide 0.6 Gm. every four hours was started. On April 21 x-ray therapy was started on the right foot, and 400 R units for five treatments were given. No other lesions received x-ray treatment.

By April 27 the patient's general condition had improved. The appetite had been good, and she had gained 4 pounds in weight. Blood sulfanilamide levels on April 17 and 20 were 4.9 mg. and 7.1 mg. per cent, respectively. All lesions showed definite improvement. The lesion on the face was much smaller. The two lesions near the right nipple were almost completely healed. The lesion over the sternum

Fig. 2.—Photograph showing healed lesions of chest and face, April 29, 1940.

Fig. 3.—Photograph of foot, April 29, 1940.

had begun to be covered with epithelium. Also, the foot showed improvement. A chest plate on April 28 showed distinct improvement in the pathologic change in the lungs. On April 29 the sulfanilamide was increased to 4.5 Gm. daily without any evidence of intoxication. The blood levels on this dosage were around 9 and 10 mg. On May 19 the sulfanilamide was reduced to 3 Gm. daily; on June 11 the dosage was reduced to 1.5 Gm. daily; and on June 27 it was reduced to 0.9 Gm. daily. In summary, this patient received sulfanilamide for a total period of eighty-three days. The hemoglobin level remained well above 10 Gm., and there was no reduction in the white blood cell count. The appetite remained good, and there was no nausea or vomiting.

X-ray examination of the right foot on June 14 showed marked improvement. X-ray examination of the chest on June 19 showed some improvement over the marked improvement noted on May 19.

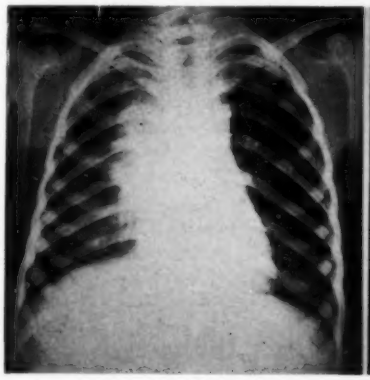

Fig. 4.—X-ray of chest, April 15, 1939.

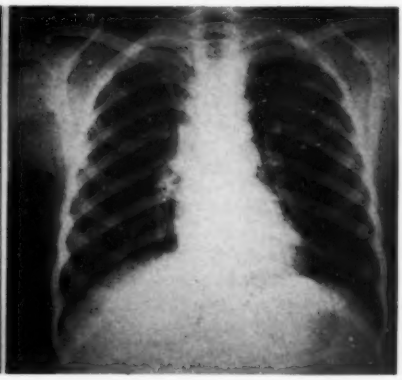

Fig. 5.—X-ray of chest, August 2, 1939.

The patient was discharged on the ninety-fourth hospital day with all skin lesions healed except for small areas over the sternum and on the right foot. She had gained 15 pounds in weight and was greatly improved in general.

She was seen in the outpatient department on August 2, at which time the lesion on the right foot was still draining slightly.

Second Hospital Admission.—The patient was admitted on Oct. 17, 1939, and discharged on Nov. 4, 1939. She was readmitted with the complaint that the lesion on the chest continued to "pile up and break down." Also, she had been having boils and at that time had two on the right arm and one on her neck. Over the sternum was a heaped-up mass without drainage. On her right foot the lesion still had a little drainage. There were two red, swollen, tender areas on her right forearm and another one below her left scapula. Cultures from these abscesses were positive for *Staphylococcus aureus*, but no *Actinomyces bovis* was found. Hot packs were applied to these lesions. The crusts on the chest were removed, and the area was cauterized with silver nitrate. She was discharged with a diagnosis of furunculosis and not a recurrence of the actinomycosis.

On April 29, 1940, she was seen in the outpatient department. At this time only scars remained over the areas which were previously draining. She had continued to gain weight and was in good general health. An x-ray examination of the chest showed that the area of density and fibrosis in the right upper part had almost completely disappeared.

COMMENT

A case of widespread actinomycosis involving the lung, chest wall, cheek, soft tissues of the hip region, and metatarsal bone in an 11-year-old girl is described. A complete cure was obtained after a long period of treatment with sulfanilamide.

Recent reports of the treatment of actinomycosis with sulfanilamide and sulfapyridine indicate that the therapy is effective.

It seems that the drug should be continued over a period of several weeks in adequate doses before this form of treatment is abandoned as ineffective.

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Critical Review

ELECTROENCEPHALOGRAPHY

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A COMPLETE review of the literature on electroencephalography would at the present time be extremely diffuse and nearly impossible, since many contributions are being made to the subject from many different points of view and covering specialized aspects. The present review will attempt to consider the subject as it seems applicable to pediatrics, trying mainly to consider the nature of an electroencephalogram and its uses in clinical pediatrics.

Electroencephalography is essentially a new method of recording a process which, though long known to exist, has been studied very little until the past decade. As Walter[74] points out in his review, such a technical development is likely to raise more questions than it answers.

Although Fleischl von Marxow had observed electrical discharges from the unopened skulls of animals, Berger[9] was the first to describe and study intensively electrical discharges registered from the unopened human skull. Since his early records were made by means of a simple galvanometer, however, the deflections registered were so small that not much credence was given them. At the present time, records are obtained by the use of complex amplifying systems attached to the scalp by a number of electrodes.[7, 37, 60] The engineering features of such amplifiers are outside the scope of the present review. Suffice it to say that their design is now well standardized and that satisfactory instruments must be capable of recording as a graph on moving paper or film, without distortion, changes in potential varying in amplitude between five and one or two hundred microvolts and in rate between one in several seconds to fifty or sixty a second. Several completely independent channels must be able to record simultaneously, and facilities allowing continuous observation over periods measured in fractions of hours must be provided. An ink writing oscillograph[25] makes long records more practicable and cheaper as compared to a cathode ray oscillograph, and is capable of recording all frequencies of demonstrated value in the investigation of abnormal cerebral states.

Such amplifying systems will record any changes in potential occurring at their electrodes, and many extraneous sources of electrical disturbances will appear unless great care is taken to exclude them. The commonest and sometimes most troublesome is radiated interference from alternating current or diathermy machines and the like, but the movement of any electrically charged body such as a celluloid ruler in the neighborhood of the electrodes, will cause artifacts in the record. Walter[74] suggests that radiated interference can be best tracked down with a portable radio set; it is in part dissipated by a grounded electrical screen surrounding the patient.

Muscle spasm produces very rapid changes in potential which may reach the electroencephalographic electrodes from the muscles of mastica-

tion or the frontalis muscle and appear in the tracing as very rapid spikes of rather wide amplitude.

Movements of the eyeball, usually accompanying blinking movements of the lids, produce rather large smooth waves, most prominent in tracings from the frontal region, less so in the parietal region, and not observable in the occipital region. Any strange waves appearing solely in the frontal region, especially if bilateral, must be suspected as resulting from movement of the eyeballs or eyelids. In cases where the observation may be important, the presence or absence of such movements must be recorded by a special observer or by special devices. The waves are due to the fact that the eyeball is not isoelectric, the retina being electronegative as compared to the cornea.[55]

Variations in the contact between patient and electrodes may result from movements of the patient, sweating, the psychogalvanic reflex, and the like. Sometimes one, sometimes all, electrodes are affected, and the result in the tracing may appear in one or all leads. Careful application of electrodes will diminish them; when they occur they are arrhythmical and unpredictable.

Exposure of silver-silverchloride electrodes to sunlight will cause photoelectric potentials to appear and distort the record.

Touching of the grounded screen by the patient will also cause wide swings of the record, usually blotting out anything resembling an electroencephalogram.

Finally, a mysterious, rhythmic, small discharge, simultaneous with the pulse beat, may occur, usually in subjects with arterial hypertension. It is not an electrocardiogram, for in simultaneous tracings it follows the latter by a short interval; it cannot be obtained in relation to pulsation of arteries elsewhere in the body but apparently is related to pulsation of the arteries in the head, since it occurs simultaneously with the latter.

Constant vigilance to discover and discount any and all of these artifacts is necessary before one can accept a tracing as being truly representative of the bioelectric discharges from the brain. Walter[74] discusses them more fully in his review. Two somewhat different systems for the application of electrodes to the patient are used. The so-called monopolar system records the differences in potential developing between an electrode attached to the scalp and to some electrically stable region of the body, such as the ear lobes or mastoid tip. Used in this way, the instrument records differences in potential that might be likened to the height above or depth below sea level on a topographic map but is more or less influenced by all the electrical discharges taking place between the two electrodes.[37] The bipolar method records the differences in potential between two points on the scalp, both of which are electrically active. The resultant graph records the difference in potential between any two points, just as on a topographic map one might count the contours between any two points on the map and know how much higher or lower one was than the other. Such records give no reference to any electrical base line but are most useful in locating foci of activity through the phase relation of the waves recorded or by localizing certain waves in certain anatomic regions.

Berger's[9] early conclusion that the electrical discharges he was recording from the surface of the head were cortical in origin was received with skepticism, although it was supported by adequate evidence. Adrian[1-4]

began soon after to study electrical discharges in the very simple nervous systems of insects. He found that groups of spikes of negative electrical discharge were given off rhythmically by the motor nerves of caterpillars and that these groups of spikes occurred at a rate fairly synchronous with the crawling movements of the animal. As soon as the ganglia of the nerves were destroyed, the spikes of negative discharge ceased. In dissections of the water beetle, Adrian showed that spikes of negative potential appeared in groups in the thoracic motor nerves of the isolated nervous system at a rate corresponding to the respiratory movements of these animals. Further investigation showed that the ganglionic portions of the nervous system developed rhythmic waves of negative potential, and that the groups of spikes of negative potential in the nerve fibers occurred during negative waves in the ganglia. He concluded that the negative waves in the ganglia were caused by periodic polarization and depolarization of the dendritic portion of the nerve cells composing them. He next showed that the resting retina of the water beetle gave rise to similar negative waves, and that illumination of the retina, if equal throughout the field of vision, caused the retinal waves to become steeper and higher, a change accompanied by the appearance of groups of spikes of negative potential in the optic nerves at a rate corresponding to the oscillations in the retina. Finally, if the illumination of the retina was patterned in any way, the recordable potential changes in the retina and optic nerves disappeared.

Since these observations, many cellular parts of the nervous system of various species have been shown to act as bioelectric oscillators. Adrian and Buytendijk[5] demonstrated this property for the isolated respiratory apparatus in the brain stem of the goldfish; Speigel[70] showed that excised bits of cortex suspended in isotonic saline solutions showed rhythmic waves of negative potential; and Heinbecker[35] demonstrated the same property in isolated nerve cells. There is, therefore, ample evidence that nerve cells are electric oscillators having periods of their own.

While this evidence was accumulating, Berger[10, 10a] had published several papers and had worked out a theory to account for the electroencephalogram as recorded from the scalp. Working with two electrodes, one occipital and one frontal, he showed that the normal adult human being examined in a quiet room, with eyes closed, produced bursts of a quasi-sinusoidal electrical discharge with a frequency of about 10 a second and an amplitude of 0 to 100 microvolts. This he called the alpha rhythm. In addition, he described a second set of waves with a frequency of about 25 a second and an amplitude of only a few microvolts and called it the beta rhythm. He concluded that the discharges were the results of the activity of the cortex as a whole. Adrian and Matthews[6] and Adrian and Yamagawa[8] studied the alpha rhythm with multi-channelled amplifiers and concluded that in their subjects it was produced by a relatively small focus in the occipital lobes, since it was largest in this region, and that it was produced by a large group of cells having to do with vision and beating in unison by virtue of the fact that they were resting, the eyes being closed. Like Berger, they observed suppression of the alpha rhythm when the eyes were opened, unless in total darkness or in an absolutely uniformly lighted field. They were able to "drive" the alpha rhythm by means of a uniformly lighted flickering field, the alpha rhythm following the rate of flicker up to rates very considerably above the spontaneous rate. In their opinion,

the suppression of the alpha rhythm was an expression of the fact that the cells concerned with vision, when functionally active, were caused to assume variable rates of electrical oscillation, with the result that no recordable variations in potential appeared at the surface of the scalp. Such a hypothesis also helped to explain Adrian's observations in regard to the retina and optic nerves of the water beetle. In addition, they showed, as had Berger, that mental effort, such as mental arithmetic, sudden startle reactions, and loud noises, tended to suppress the alpha rhythm. Adrian believed that the alpha rhythm spread by electrical transmission from the occipital focus, and that no other sufficiently large areas of the brain developed electrical synchronization to produce recordable changes in potential at the surface of the scalp.

Various observers have made observation showing conclusively that other areas of the cortex can produce alpha rhythm, and that it is not always in phase in the two hemispheres. Jasper and Andrews,[38] with bipolar electrodes and carefully controlling their observations, reported that alpha rhythm could arise in the precentral region as well as the occipital. The differentiation between the occipital and precentral alpha depended on the fact that bursts of one sometimes occurred independently of the other, and that modifications of the two rhythms occurred sometimes in one, sometimes in the other, and sometimes in both in response to a variety of stimuli. On the whole, the alpha rhythms tended to be synchronous in the two regions.

Making use of the fact that the alpha waves tend to occur in bursts with relatively quiet periods between, Rubin[62] studied the "per cent time alpha" in tracings taken simultaneously by eight electrodes, all recording against an indifferent electrode. He found that alpha rhythms were produced characteristically in the occipital and frontal regions, and that for any individual the per cent time alpha in the occipital region was very stable, whereas, in the frontal region this was not the case. Furthermore, he found that the bursts of alpha rhythm were not synchronous in the two occipital lobes, a finding more or less in consonance with Jasper and Andrews'[37] statement that there was no constant phase relationship in the alpha rhythm produced by the two occipital lobes. Walter,[74] however, reported that in about 1,000 subjects the foci of occipital alpha were nearly always symmetrical, that the rate was nearly always the same on the two sides, and that the waves were practically always in phase on the two sides. It seems very difficult to reconcile these divergent statements of apparent facts, but it is probable that the bipolar records of Jasper and Andrews cannot be compared in this respect with the monopolar records reported on by Walter, since slight changes in the position of a pair of electrodes might very well change electrical relationships.

Jasper and Andrews[38] reported that the typical discharge from the precentral regions was fast in rate and small in amplitude, about 25 oscillations per second at an amplitude of a few microvolts, corresponding to Berger's beta rhythm. They reported that these waves were more readily suppressed by tactile stimuli than others and occasionally arose in the occipital region as well. They felt that on the whole the alpha rhythm tended to occur at the back and top of the head, while the beta rhythm was seen mainly on the top and front of the cranium, a conclusion in which Loomis, Harvey, and Hobart[59] concur.

Although Adrian and Matthews[6] reported absence of alpha rhythm in blind persons, Berger[13] recorded quite normal alpha rhythms in such subjects. Loomis, Harvey, and Hobart[56a] showed that sounds quite inaudible to the average person had sufficient "arousal value" to completely block the rhythm in blind subjects. In working with such subjects, it is therefore most important that extra precautions be taken to gain their confidence in the procedure, lest anxiety due to unexpected causes evoke cerebral activity sufficient to suppress the normal rhythms.

There is great variation from person to person in the character of the electroencephalogram; certain individuals show nearly continuous alpha activity under standard conditions and others show almost none. All degrees between are encountered. In good health the rate for a given adult is very stable, varying by less than 5 per cent, and in adults generally it lies between 8 and 13 oscillations per second. Davis and Davis[17] concluded that the cortical electrogram reveals some inborn pattern or feature of cerebral activity, one important feature of which is its lability. They also showed that its pattern conforms to the biologic law of identity in identical twins.

Although the pioneer work of Berger, Adrian and his co-workers, and Jasper and his group, to mention a few, had pretty convincingly demonstrated the cortical origin of the electroencephalogram, animal and surgical experiments proved the point. Kornmüller[43] had shown diverse types of discharges from various cytoarchitectonic fields of the cortex of anesthetized or curarized animals. He discussed two types: one, the spontaneous or autonomous discharge of the resting fields, or "Feldeigenstrome," and the other, discharges resulting from stimulation elsewhere, or "Feldreactionstrome." For the most part clinical electroencephalography deals with the former type of discharge. Kornmüller[44] also demonstrated that electrophysiologic disturbances in a given area of one cerebral cortex caused by painting it with strychnine solution were mirrored in homologous areas of the opposite hemisphere. Rheinberger and Jasper,[61] by imbedding electrodes between the skull and dura of cats, obtained simultaneous records from four different areas in unanesthetized cats over periods of hours or days. Though some fairly consistent differences in the pattern of activity could be identified with different cortical fields, the variations in activity in each region in the normal cat were so great that bioelectric differentiation appeared to be primarily related to different states of activity rather than to cytoarchitecture. The electrogram from all regions was characterized by low amplitude and high frequency when the cat was aroused either by external stimuli or internal organic states, such as the need for defecation or urination. Relaxation, on the other hand, was associated with a return to wider amplitude and slower rhythm. Although changes in the electrical activity of the entire cortex usually followed any effective stimulus, the changes in a given region could be more intense or of a different form from those in other fields. In these animals bilaterally homologous areas showed essentially similar bioelectric phenomena. At surgical exploration, Foerster and Altenberger[24] used cortical electrodes and obtained tracings similar to those obtained from the overlying scalp but 50 to 100 times the amplitude recorded at the surface. Their records from various cytoarchitectural fields were very similar. Walter[72] reported similar findings with electroencephalograms made with electrodes in the cortex at operation.

Grass and Gibbs[34] in 1938 described a new method for the study of electroencephalograms. By means of a photoelectric filter, a Fourier transform of the record is made, resulting in a graph or spectrum showing the amount of energy given off at various frequencies. By means of this device, they showed that energy is given off from the head over a wide range of frequencies, but that concentrations of energy emanation occur at frequencies between 1 and 12 cycles per second and between 18 and 22 cycles. Examination of such spectra shows the futility of attempting to classify alpha, beta, and other waves too rigidly. The use of such a transform does not permit the detection of short bursts of abnormal waves, and for this purpose the unanalyzed record continues to be necessary.

Using such a transform to study the electrical energy emanating from the head, Gibbs[26] reached certain rather fundamental conclusions. He considered the brain cells to be low-power oscillators which might link together to form powerful oscillators. Cortical activity, according to him, should be regarded as the product of a whole mass of oscillators whose activity can be expressed only as a spectrum of frequencies. Normal cortical activity is carried on within certain limits of energy distribution over such a spectrum. A moderate shift in activity toward the fast end of the spectrum of cortical frequencies is associated with rapid motor responses, an extreme shift with convulsions and unconsciousness. A shift toward the slow end of the spectrum is associated with slowing of voluntary motor activity and slowing of mental processes, and a more extreme shift is associated with stupor.

In general, it seems fairly certain that complex cortical function breaks down what appear to be spontaneously aggregated large oscillators formed of many cells, into smaller oscillators whose emanations are either so small that they are lost in the process of transmission through the skull and scalp, or which tend to obscure each other because of their lack of synchronism. The most prominent oscillators appear in pairs and are most frequently occipital, precentral, and frontal. In general, the occipital and frontal regions tend to produce waves at a rate of about 8 to 13 per second, while the precentral area is frequently a center for more rapid waves. From one individual to another these vary widely, certain individuals showing almost no alpha under any circumstances, and many showing no beta waves.

The phenomenon of sleep has been studied by a number of investigators. Loomis, Harvey, and Hobart[57, 58] found that the transition from the waking to the sleeping state was characterized by five steps. Beginning with the normal alpha rhythm when awake, the first change was the appearance of periods of suppression of the alpha waves which coincided with the sensation of floating off in the subjects. Next, low voltage slow waves at a rate of 2 to 5 per second appeared; these investigators called these waves delta waves, the name given by Walter to similar waves recorded from the neighborhood of tumors. The third step was marked by an increase in the voltage of the delta waves up to about 150 microvolts, and the appearance between them of "spindles" of waves with a rate of 14 per second, the spindles being short bursts of waves beginning at a small amplitude, increasing rapidly in amplitude, and then dying out. The fourth stage is marked by an increase in the size and irregularity of the delta waves and in the prominence of the

spindles. Finally, the spindles drop out irregularly, and there remain very large, random delta waves.

Blake, Gerard, and Kleitman[14] followed the progress of sleep throughout the night and pointed out that there was a sort of ground plan or evolution of the potentials on which minute-to-minute variations were superimposed, starting with the alpha rhythm, a phase of alpha plus delta, then delta alone, then a null period with very little activity, and then gradually intermittent bursts of poorly defined alpha during the light sleep of early morning. The 14-per-second spindles tended to appear during the early portion of the evolution. The period of diminishing depth of sleep did not mirror the period of increasing depth of sleep. Blake and his co-workers felt that subjective reports of dreams could be related to electroencephalographic changes, and that movement tended to alter the potential pattern toward that of lighter sleep. Hypersomnia, induced by a long experimental period of wakefulness, or narcolepsy was associated with delta waves at higher levels of consciousness than normal sleep. A stimulant drug, benzedrine, tended to abolish delta waves, and a depressant drug, alcohol, tended to increase them. In the light of these findings, these investigators discussed theories of sleep.

During sleep there recurs from time to time a prominent pattern which is related to so-called on- and off-effects seen in the waking electroencephalogram. Davis[20] discussed these on- and off-effects seen in monopolar records from the vertex and occiput of waking human subjects. Acoustic stimuli were frequently followed by a diphasic or sometimes triphasic wave most prominent over the vertex and of a duration approximating 0.3 seconds. The voltage from peak to trough varied from a just discernible deflection to 100 microvolts. Frequently there was a similar off-effect of less intensity. Occasionally, checking of the alpha or beta rhythm was the only effect. Anticipatory on-effects could be produced by a regularly spaced series of sounds when the spacing was suddenly varied or the series ceased, the subject not expecting it. When the condition of the subject changed from alertness to drowsiness, the reliability of the on-effect and the predictability of the anticipatory on-effects were enhanced. These on- and off-effects were recorded simultaneously over all parts of the cortex.

Loomis, Harvey, and Hobart[59] considered the distribution of disturbance patterns in the human electroencephalogram, with special reference to sleep, by means of six simultaneously recorded channels, using the monopolar method. In waking subjects they found that the right and left halves of the head were fundamentally alike in pattern but that front, top, and back might be quite different; the beta rhythm appeared most convincingly on the front and top of the head, the alpha rhythm on the top and back of the head. Except for potentials resulting from eye movements, they found no evidence of electrical spread. Very large areas exhibited the same pattern or frequency which was often synchronous and in phase on the two sides and less often out of phase and of slightly different frequency. In the early stages of sleep the pattern reflected the normal waking pattern of the individual, but in the deeper grades of sleep they found all persons to be alike, with delta waves all over the head and 14-per-second waves predominant on top of the head. A disturbance affecting the alpha in waking subjects usually affected all of the regions showing alpha rhythm simultaneously, but delay in the effect on the alpha might appear in certain regions. A disturbance

during sleep always affected all regions of the head simultaneously and might be either a return of the alpha rhythm, the appearance of large 7-per-second waves, or what Loomis and his associates called the K complex. The latter appears as a large diphasic wave, negative with respect to the ears, and superimposed upon it might be 14-per-second waves. It regularly appeared after tone stimuli, sometimes seemed to appear spontaneously, and it was in greatest amplitude on top, less in front, and least on the back of the head. They concluded that during sleep the cortex acts as a whole.

Davis, Davis, Loomis, Harvey, and Hobart[19] studied the electrical reactions of the brain to auditory stimuli during sleep and found that the K complex was regularly evoked by sound in moderate stages of sleep, but that other stimuli, such as electrical shocks or light, produced less marked or reliable K complexes. They described a fast component of the K complex best seen over the central portions of the cortex and a more prominent slow component over the frontal portions. They concluded that the depth of sleep also had a bearing on which component appeared most prominently. The subjects were not necessarily awakened or aroused by the stimuli producing the K complex.

They evolved a chart (Table I) to describe the changes in the electroencephalogram produced by various stimuli in relation to the psychologic set of the subject. The alpha optimum state they considered to be that of wakefulness but with the mind blank.

TABLE I

	ALPHA		ON-EFFECT TO SOUND
	EYES CLOSED	EYES OPEN	
Alert	Present as usual	Alpha checks sharply	Alpha check; on-effect or no effect
Alpha optimum	Maximum	Alpha check not so clear cut	On-effect more reliable
Drowsy	Reduced and variable	Alpha returns	Higher voltage on effect
Sleep	Absent		On-effect becomes the K complex

From Table I it is evident that various psychologic states show not only diverse electrophysiologic expressions, but that the same stimuli may produce effects which are quite different in the various states.

Davis, Davis, Loomis, Harvey, and Hobart[18] considered the changes in the electroencephalogram during the onset of sleep and concluded that during clinical study (presumably in adults), the drowsy state must be strictly avoided because of the similarity of the patterns of very early sleep to those described for many abnormal conditions.

Changes in various physiologic constants have effects on the electroencephalogram. Gibbs, Davis, and Lennox[28] reported that during unconsciousness resulting from breathing pure N_2, the waves became larger and slower (2 to 5 per second), and that overventilation caused larger than normal waves, which at first were faster than normal (10 to 20 per second) and later slower (about 5 per second) when the subject became confused. Hoagland[36] has shown that the alpha rate is increased in fever, and Jasper and Andrews confirmed this. Gibbs, Williams, and Gibbs[32] reported on changes in the frequency spectrum

in Fourier transforms of the electroencephalogram resulting from changes in blood carbon dioxide, sugar, and oxygen content. Decrease in carbon dioxide was associated with a shift of energy distribution toward slower activity; increase in carbon dioxide, with a shift toward the fast side. These effects were less marked after extreme than after more moderate variations in carbon dioxide. Oxygen and sugar concentration in the blood, on the other hand, could be varied within wide limits with little or no change in the cortical frequency spectrum, but when the oxygen saturation or glucose concentration fell below a critical level, there was a sudden shift of energy distribution to the slow side. With exceedingly high concentrations of glucose the energy distribution in the cortical frequency spectrum shifted toward the fast side. Experiments on rabbits indicated that extremely high oxygen tensions were similar in their effects. They concluded that the electrical activity of the cortex was a manifestation of the activity of a great number of chemical oscillators having different natural periods. Although they differed in their periods, these oscillators tended to respond similarly to any given factor, and although any factor tended to affect all frequencies in the same direction, it did not necessarily affect all to the same degree. As a shift toward faster frequencies occurred, the amount of energy registered by the electroencephalogram became less, perhaps an effect of oscillators in general and of diffusion in chemical oscillators in particular.

Certain drugs known to affect the nervous system cause changes in the electroencephalogram. The fat solvent anesthetics, ether and chloroform,[9, 73] tend to produce large slow waves; Rubin and Freeman[64] reported a series of changes in the electroencephalogram due to cyclopropane anesthesia somewhat reminiscent of those occurring in sleep but occurring at different times from various areas of the scalp. Barbiturate anesthesia[73] produces very prominent waves at the lower frequencies found for the alpha rhythm in adults. As sedatives, little or no effect is produced by barbiturates. Alcohol consumed in ordinary amounts enhances the prominence of the alpha rhythm; in larger quantities it tends to slow it, and in acutely toxic doses it produces large slow waves.[56] Bromides tend to slow and accentuate the alpha rhythm in normal subjects.[47] Libet and Gerard[50] studied the effect of various chemical ions, drugs, and physical changes on the electrical discharges of isolated frog brains.

The convulsant drugs also affect the electroencephalogram. Kornmüller[44] found that local applications of strychnine to the cortex produced a local discharge of waves at a frequency of 2 to 6 per second, and that a similar discharge appeared in the homologous region of the cortex on the unstimulated side. Gozzano is quoted by Walter[74] as stating that the discharge so produced in the unstimulated cortex was prevented by cutting the corpus callosum. Dusser de Barenne and McCulloch[22] showed that strychnine applied locally to nervous tissue produced "firing" of the cell beyond the synapse but only in the normal or dromic direction from the cells originally stimulated with strychnine. If the local application of strychnine was made to the motor cortex, convulsive movements of the limbs resulted.

The injection of cardiazol in schizophrenics was studied by Cook and Walter.[74] The injection was followed by large waves given off from the whole cortex at a rate of about 5 per second; if a convulsion supervened,

a sudden greater outburst of activity appeared, spreading from the frontal region over the cortex, increasing in size and decreasing in frequency as it did so. Lemere[46] found that following the treatment of schizophrenia by convulsant drugs, the electroencephalogram was more or less permanently altered, with a tendency toward enhancement of the alpha rhythm and a loss of delta activity. His tracings certainly suggest a change in cerebral physiology, though it is not as yet clear whether such changes are desirable. Lennox, Gibbs, and Gibbs[47] studied the effect of convulsant drugs in epilepties.

The effect of many other drugs on the electroencephalogram, as for instance cyanide,[13] drugs affecting the sympathetic nervous system,[33] endocrines, etc., has been studied; in general, slight if any changes were found. Golla, Graham, and Walter[33] reported that benzedrine tended to abolish the abnormal discharges seen in pyknolepsy in children, but this effect, so far as I know, has not been reported by others. In a few instances which seemed to me to fulfill the criteria for a diagnosis of pyknolepsy I have administered the drug in graduated doses up to tolerance without any effect on the clinical attacks.

The electroencephalogram in children has been studied by a number of observers. Berger[11] reported no activity in a one-month-old infant and the gradual development of an alpha rhythm assuming adult features at 5 or 6 years of age. According to Walter,[74] he, with Golla and Graham, plotted the alpha frequency against age in a large series of normal individuals and found a flat-topped curve extending from 10 to 65 years of age, with a sharp decline to slower frequencies at both ends of this plateau, even though all the older subjects retained their faculties very well. Smith[65] studied the electroencephalogram in early infancy and found that in the newborn infant no electrical activity could be recorded from the scalp while the infant was awake. During sleep, however, he found electrical activity present over the sensorimotor region of the cortex and not elsewhere; the activity ranged in rate from 1 to 20 cycles per second and occurred in special bands 1 to 3 per second (delta waves), 3½ to 6 per second (especially prominent during the drowsy state), 7 to 8 per second, and 12 to 14 per second (which he identified with the spindles of adult sleep). During the early development of infancy, these waves increased in amplitude, in length of rhythmic sequence, and in regularity, reaching a peak at about 4 to 6 months of age. Thereafter three of the rhythms, 1 to 3 per second, 7 to 8 per second, and 12 to 14 per second, remained unchanged, while the 3½- to 6-per-second drowsy waves tended to drop out. In a second article Smith[66] studied the nature of the growth of the alpha rhythm. For this purpose the infants were examined while awake in a darkened room. The alpha waves began to appear in a pair of occipital leads at about 3 months of age and were first noted just before the infant became drowsy. The sensorimotor drowsy waves always appeared with or soon after the alpha waves at this age. During the next several months the runs of alpha before drowsiness increased in length and rate so that by about 1 year of age, a well-established alpha at a rate of 5 to 7 cycles per second was usually found. It continued to increase in rate as age increased, so that by 8 years of age it reached the adult rate of 8 or 9 cycles per second. In spite of its gradual change in rate, the infantile alpha rhythm was extinguished by the same factors that extinguish it in the adult. Smith called attention to the difference

between the sensorimotor drowsing and sleep waves which remained at the same rate, though increasing in prominence throughout infancy and childhood, and the occipital alpha waves which increased both in prominence and rate throughout infancy and childhood. Smith[67] also studied the development of the pattern sequence occurring during the transition from waking to sleeping. During the early weeks of infancy no special pattern was found, but with advancing age the 3½- to 6-per-second waves tended to be pushed into the drowsing period before sleep, while the delta waves (1 to 3 per second) tended to appear only after sleep had been well established; the 12- to 14-per-second waves appeared in conjunction with either type. By the time the infant showed a well discernible alpha rhythm (5 to 6 months of age) its disappearance preceded the appearance of the 3½- to 6-per-second waves, and the adult awake-sleeping sequence was fairly well established. Smith wondered whether the 3½- to 6-per-second drowsy waves might not be the same as the delta waves which observers of adults had noted in conjunction with the alpha of early sleep.

Lindsley[51] studied the electrical potentials of the brain in normal adults and children. He found that his group I waves (which correspond to the alpha rhythm of other observers) appeared first at about 3 to 4 months of age at a rate of 3 to 4 cycles per second, and increased rapidly in rate with advancing age to an average of 7 per second at 2 years of age, 9 per second at 8 years of age, and 10 per second at about 20 years of age. His type II and III waves (apparently identical with the beta rhythm) were present in the occipital leads at birth and changes in their rates were not discussed. He also reported on waves at other frequencies that tended to increase in rate with age. He recorded the alpha rhythm simultaneously from both occipital regions and reported that the waves from the two cortices were usually in phase but that occasional records showed frequent shifts in the phase relationships and that brief periods of asynchronization did occur. In 1939 he[52] reported a more extensive longitudinal study of the frequency of the alpha rhythm as observed by bipolar electrodes 5 cm. apart over both occipital regions, and he reported essentially the same rate findings. The earliest alpha appeared at 3 months of age, with a rate of 3.5 to 4.5 per second, increasing at the end of the first year to between 5.5 to 7 per second, and at the end of five years, 7.3 to 8.8 per second, with an average of 7.9 per second, just below the lower limit of adult normal rates. At 12 years of age the adult range of 8 to 12 cycles per second was reached. The amplitude of the waves tended to be large in the early months, reached a maximum at about 2 years of age, and thereafter declined sharply, apparently in relation to the closure of the sutures and fontanels. During the first two years he found amplitudes of 30 to 50 microvolts; by 3 years of age the voltage was always below 30 microvolts, and reached the adult range of 10 to 16 microvolts at about 16 years of age. He felt that the increasing frequency and decreasing amplitude might be the result of the interaction of several factors.

Weinbach[75] took Smith's and Lindsley's data for the increase in rate of alpha waves and compared them with standard figures for the increasing weight of the brain with respect to age. Both sets of data produced similar curves, and Weinbach derived a formula by which the average weight of the brain at a given age could be derived from the average alpha rhythm at the same age. He felt that the increase in

weight of the brain after birth and the alpha rhythm were different expressions of the growth process which were closely related.

Smith[68] compared the development of the alpha rhythm in the precentral and occipital regions and found that their developmental patterns with respect to age were different and concluded on the basis of these data that the occipital and precentral alpha rhythms were derived from different foci. Lindsley[53] felt that four different foci of alpha rhythm in each hemisphere could be distinguished, two in the occipital region, and one each in the temporal and anterior parietal regions.

Knott and Gibbs[42] made a preliminary report on Fourier analyses of electroencephalograms from one to eighteen years. They collected data for right and left occipital, motor, frontal, and temporal leads from 130 normal children and reported analyses by the Grass photoelectric transformer for the left occipital tracings only. At 1 year of age the transforms indicated a high energy output at about 6 cycles per second and an absence of any well-defined peaks. With advancing age, there appeared to be a gradual emergence of energy peaks in the so-called alpha (8 to 12 per second) and beta (18 to 30 per second) frequencies. The authors reported that they intended to complete these studies for all the leads and relate them to transforms of data from similar leads in adults.

In general, it appears that the electroencephalogram varies with age, and that at birth little or no output of energy can be recorded; then rapidly increasing energy output is evident, accompanied by increasing organization which attains adult characteristics for sleep in the first two or three years of life, and for the occipital alpha rhythm between 5 and 8 years of age. Some rapid activity in the beta range (18 to 30 cycles per second) is present soon after birth, but the energy output in this range may increase with age although its rate does not vary much.

In abnormal conditions the electroencephalogram varies from the normal pattern chiefly when the cortex is involved. Many conditions have been investigated and will not be reported on; only such subjects as show definite abnormalities or are of special pediatric interest will be considered. The outstanding abnormal findings are in relation to increased intracranial pressure, tumors, cysts, scars, or abscesses invading or compressing the cortex, the epilepsies, and certain intoxications, inflammations, and behavior problems.

Increased intracranial pressure from such causes as obstruction to the channels conducting the cerebrospinal fluid, tumors, concussion, and meningitis is accompanied by large slow waves, at about 3 cycles per second over the whole cortex.[72, 73] The waves were reported by Walter as resembling those seen during ether anesthesia, often showing a deflection of as much as 100 microvolts. In Walter's reports it appears that the prominence of the abnormal discharge is more in relation to the degree of disturbance of cortical function than to height of intracranial pressure. It would thus appear that the electroencephalographic investigation of infants with hydrocephalus would be disappointing, since the electrical activity, if present at this age, tends to be slow normally.

Cerebral tumors provide one of the most striking examples of the clinical usefulness of electroencephalography. Berger[12] reported a few

cases, but he did not use the multiple channel method of localization which Walter so successfully demonstrated in 1936 and 1937. In the first of these papers Walter reported on electroencephalographic tracings from seven cases of cerebral tumor; in certain instances tracings were taken from the intact scalp and then from the exposed brain, as Foerster and Altenberger[24] had also done. Such tracings were similar, save that those taken directly from the cortex were ten to fifty times greater in amplitude than those taken from the scalp. The tumors themselves were inactive electrically, but the surrounding intact appearing cortex gave off abnormal waves. As recorded from the scalp, these appeared as waves at a rate of 2 to 3 cycles per second at an amplitude of 10 to 20 microvolts, provided the cortex was affected by invasion, pressure, or atrophy. Dusser de Barenne and McCulloch[21] have shown since that slow waves can be produced by partial coagulation of the monkey's cortex. Walter called them delta waves and showed that, unlike the alpha rhythm, they were not extinguished by light, thought, or vision. In his second paper Walter amplified these findings in a group of thirty-eight suspected tumor patients. He found a focus of delta waves in twelve patients and all of these had tumors at the site of the focus. In twenty-six no abnormal focus was found, and among them were two cerebellar tumors and one eighth nerve tumor but no other tumors.

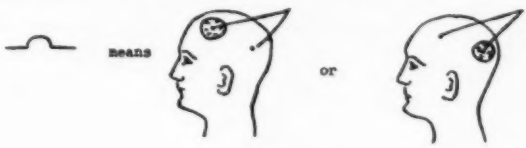

Fig. 1.

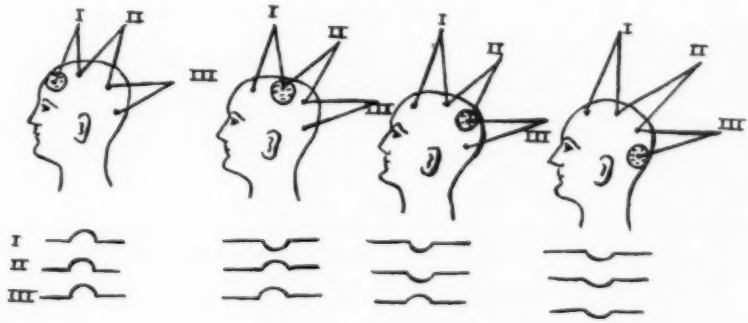

Fig. 2.

Walter showed how a delta focus might be localized and Figs. 1 and 2 are diagrams taken from his paper. In the electroencephalogram the length of the upward deflection is proportional to the time required for the indicated electrical disturbance to pass on or die out. With four electrodes it is possible to show where the focus is, and hence its polarity (Fig. 2).

This method can be applied to a series of electrodes placed either sagittally or coronally and serves to localize foci of abnormal discharge very accurately.

In his patients Walter showed that increased intracranial pressure with its generalized delta discharge obscured such a focus, but that relief of the pressure by dehydration or hypertonic solution often made possible the elucidation of the focus.

It should be emphasized that Walter's patients were examined because of the suspicion of intracranial tumor, and that foci of abnormal waves can be detected in other conditions, especially the idiopathic epilepsies.

Williams and Gibbs[76, 77] made two reports on the localization of cortical lesions by electroencephalography. In a random sample of eighty cases, mostly referred by neurosurgeons, they found thirteen individuals with records characteristic of epilepsy and without any constant focus of abnormal discharge; in seventeen more cases no abnormality was found. Among the fifty patients with localized abnormalities, no definitely diagnostic procedures were carried out, but in the remaining thirty-seven patients, definite conclusions were reached. In every case with a single focus of abnormal discharge, lesions were proved by operation, bone defect, or unequivocal x-ray evidence to correspond closely with the site predicted by electroencephalography. Tumors, scars, porencephalic defects, subdural hematomas, abscesses, Paget's disease of the skull with localized pressure and ischemia of the cortex, tuberculoma, Schilder's disease, and idiopathic local cortical atrophy were among the pathologic processes discovered at the site of the abnormal waves. Operative cortical defects were found not to produce slow waves. The absence of any localized focus after the removal of high intracranial pressure waves by hypertonic glucose correctly suggested cerebellar tumor once.

The negative cases remained negative; seven clinical diagnoses of tumor were correctly refuted by the method.

In their second report Williams and Gibbs[77] considered electroencephalography in clinical medicine. A good discussion of various methods was given, and it was pointed out that in localizing tumors both unipolar and multipolar records must be made to exclude the epilepsies and then localize a tumor. One hundred and five cases in which intracranial lesions were suspected were reported, and a close correspondence was shown between the predicted site of lesion and the actual lesion in fifty cases in which anatomical definition was obtained. In forty-one cases no abnormal focus could be found by electroencephalography or by any other method, and in fourteen, although an abnormal focus was electrically demonstrable, no adequate anatomical study was ever made.

Case and Bucy[15] reported on the localization of cerebral lesions by electroencephalography. They report six types of abnormal waves from injured or diseased areas of cortex: (1) very slow swings, 1 or 2 in five-second intervals; (2) slow waves, ½ to 3 per second; (3) spike and saw-tooth forms; (4) localized electrical manifestations of epilepsy; (5) absence on one side or marked and persistent difference of the alpha rhythm on one side as compared to the other; and (6) marked localized diminution or absence of electrical activity. It is not clear from this report that cases of idiopathic epilepsy were excluded from their series, and as will be shown, various observers report electrical localization in many cases of so-called idiopathic epilepsy.

Cerebellar tumors have been reported to show no abnormalities by electroencephalography, but Smith, Walter, and Laidlaw[69] reported a

small series of cases of cerebellar tumors in which delta waves were found in the occipital leads. They felt that these waves might be caused by pressure on the occipital lobes by the tumor mass. The rigid barrier formed by the falx and tentorium would tend, of course, to minimize or prevent such pressure until the force exerted became very great.

As indicated in Walter's second communication, tumors of the brain stem and those sufficiently deeply placed in the cerebral hemispheres do not cause any localized abnormalities in the electroencephalogram.

In the epilepsies the electroencephalogram has opened up a whole new field for exploration and has helped, in some measure at least, to dispel the frustration of the physiologist and clinician in relation to this disease. In 1931 Berger[10] reported large slow waves in cases of epilepsy complicated by mental defect. These discharges have been extensively studied and reported by Gibbs, Gibbs, and Lennox. In 1937[29] they reported 900 hours of records taken from 400 epileptic patients of whom 120 had from one to many attacks during the taking of the records. Their conclusions are herewith quoted nearly in full.

1. "Seizures involving the cortex are accompanied by distinct and characteristic fluctuations in the action potentials of the brain. (Vagal fits for instance may not involve the cortex adjacent to the calvarium.) True tonic-clonic grand mal epilepsy involves the cortex universally and a fit is always registrable.

2. "The three types of seizures (involving the cortex) have three distinct cerebral rhythms. In all there occurs a great increase in voltage. Grand mal has a fast rhythm (25 to 30 cycles per second), psychomotor attacks a slow rhythm (3 to 4 waves per second), and petit mal alternating slow round waves and fast spikes at a rate of about 3 waves and spikes per second. The stupor period following an attack is marked by relative absence of registrable electrical activity.

3. "These electrical disturbances, the cause of the externally visible evidences of epilepsy, are themselves the result of a poorly functioning hypothetical rate-regulating mechanism. Factors which tend to modify the normal electroencephalogram tend in epilepties to modify it to an abnormal degree; for instance, it is well known that the transition from sleeping to waking is frequently accompanied by attacks in epilepties.

4. "Seizure patterns were recorded while no subjective or objective evidence of seizures occurred. Such subclinical or larval seizures were of two types: (a) Abnormal patterns of the same character as those occurring during overt attacks but of lower voltage and shorter duration, such attacks being most commonly of the petit mal type and often unsuspected; (b) isolated abnormally large waves, similar to any of the patterns described.

5. "Prediction of seizures in grand mal epilepsy is possible by estimating the amount of fast activity in a fifteen-minute record from day to day.

6. "Localization of the point of origin of the abnormal rhythms is frequently possible by three-channel recording, although usually the abnormal rhythm appears over the whole of the accessible cortex simultaneously. In occasional instances the abnormal waves of subclinical seizures were entirely limited to one area of the cortex.

7. "Visualization of the effect of treatment becomes possible in the case of a patient with abnormal waves; thus phenobarbital and bromide, given

intravenously while a tracing is being made, slow the cerebral rhythm and always improve the dysrhythmia of grand mal, may or may not improve that of petit mal, and always make that of psychomotor attacks more prominent. The abnormal rhythms of petit mal tend to disappear with mental effort and do disappear miraculously with the inhalation of 7 to 10 per cent carbon dioxide. All the abnormal rhythms are enhanced by insulin and decreased by glucose."

Gibbs[27] in 1939 drew an analogy between the behavior of the epileptic discharges from the cortex and the activity of the respiratory center under various physiologic and pathologic situations. The cortical waves and respiratory rate are slowed by sleep, sedation, and low carbon dioxide level, while both rates are increased by fright, sensory stimuli, and a high carbon dioxide level. Gibbs pushed the analogy further, likening the activity of grand mal to tachypnea, both being induced by high carbon dioxide levels and prevented by low carbon dioxide levels, petit mal to periodic breathing, since both are induced by low carbon dioxide and prevented by high carbon dioxide levels, and psychomotor attacks to bradypnea, but here the study had not been carried out to allow chemical analogy.

Gibbs, Lennox, and Gibbs[31] showed that the frontal lobes were intimately connected with the source of the petit mal type of discharge. Golla, Graham, and Walter (reported by Walter[74]) felt that a localized focus of abnormal waves could be shown to occur between attacks in the various types of epilepsy. They stated that for grand mal such a focus was usually found in the region of the superior frontal gyrus, for petit mal in the postcentral region, and pyknolepsy of children in the occipital region, and they reported delta activity quite similar to that found in the neighborhood of tumors from these foci between attacks in about 50 per cent of their cases. This "resting delta activity," apparently comparable to Gibbs, Gibbs, and Lennox' second type of larval attack, could not be diminished by the use of drugs, save that in examples of pyknolepsy it sometimes vanished along with the attacks after the administration of benzedrine.

Jasper and Hawke[39] reported 117 electroencephalographic tracings from fifty-five patients with epilepsy. They were able to localize by bipolar recording the region of the head beneath which seizure waves appeared to originate. Localizing signs suggesting primary involvement of the front of the head were obtained in fourteen of thirty-seven cases of grand mal and five of eighteen cases of petit mal. The posterior region of the head appeared to be primarily involved in six of the thirty-seven cases of grand mal and eight of the eighteen patients with petit mal. Localizing signs were found in thirty-three of the fifty-five patients. Certain records reproduced in the article suggest that the focus of epileptic discharge changed its position during the course of an attack.

According to Walter,[74] he, with McKissock and Golla, showed that the existence of a cortical focus of abnormal electrical activity was not proof that the primary cause of epilepsy was in the cortex. They found that the excision of a delta focus in idiopathic epilepties was followed by a few months of comparative freedom from attacks, but that gradually the preoperative condition supervened, and the operation was no more successful than any major operative procedure. Again, according to Walter, he, with Golla and Graham, showed that the excised cortical

areas responsible for the resting delta discharge showed slight to marked histologic changes. Gibbs[27] in 1939 also stated that the removal of epileptic foci localized by electroencephalography alone was likely to be followed by disappointing results.

Lennox, Gibbs, and Gibbs[48, 49] published a preliminary report on the inheritance of the dysrhythmia of epilepsy in 1939 and a greatly augmented report in 1940. The latter is of interest from several points of view.

The first portion deals with methods of recording and of interpreting the records, and since an understanding of their conclusions is possible only in the light of these facts, they will be considered briefly. Simultaneous six-channel "monopolar" records at least 20 minutes in length and ending with a period of hyperventilation (unless attacks were recorded without hyperventilation) were made on every subject. Under these circumstances only 3 per cent of individuals with overt attacks had normal records.

According to the authors there is no rule of thumb for judging normality in records. The main factors to be considered are (1) dominant frequency, (2) constancy of record, and (3) voltage. A dominant frequency may not exist, but if it does and is below 8 cycles per second or above 25 in a subject over 12 years of age, it is abnormal. Between 11 and 15 years of age a normal dominant frequency may fall as low as 6 cycles per second, and under 5 years of age it must be 3 cycles per second or slower and of high voltage, or above 13 cycles, to be abnormal. In occasional records with normal dominant frequencies, bursts of two or more waves outside the normal range in rate and at a higher voltage than the rest of the record may appear. The larger the number of these abnormal waves during the period of observation, the more sudden the shift from the normal to the abnormal frequency, and the higher the voltage of the abnormal waves, the greater the degree of abnormality of the record. A burst of waves faster than 13 per second and increasing gradually over a period of several seconds from a low to a high voltage (over 50 microvolts), or a run of square-topped 4-per-second, or high voltage 6-per-second waves not accompanied by symptoms, was considered evidence of subclinical grand mal, or psychomotor seizures. Runs of 3-per-second wave and spike formations were considered diagnostic of petit mal. Changes in rhythm after overventilation were not considered abnormal unless they formed the typical petit mal pattern. Attacks of petit mal lasting less than three seconds were usually subclinical; the finding of one clearly defined wave and spike formation made the record abnormal. Elements which weighed in favor of a normal record were the presence of regular 9- or 10-per-second waves in the occipital or other leads and the absence of sudden shifts in frequency. The records were reread after long intervals, and only 10 per cent were changed in classification. Records showing the above abnormalities were considered dysrhythmic by the authors, and epileptic only if overt attacks occurred.

Electroencephalographic tracings were made of 183 parents, siblings, or children of ninety-four patients suffering from clinical epilepsy and cerebral dysrhythmia. These records were compared with those of a control group of 100 normal persons, none of whose near relatives had epilepsy. In the control group 10 per cent had abnormal records, 6 per cent questionable records, and 84 per cent definitely normal records.

Among the near relatives of the epilepties, 60 per cent of the records were definitely abnormal, 8 per cent were doubtful, and only 32 per cent definitely normal. In fifty-five of the families, records of both parents were obtained, and in 35 per cent of these families the records of both parents were abnormal, and in only 5 per cent were the records of both parents normal. Among the parents of patients with "symptomatic" epilepsy, dysrhythmia was as frequent as among the parents of those with "essential" epilepsy. It occurred more often among the relatives of female patients and among female relatives than among the relatives of male patients or among male relatives, indicating to the authors some sex linkage of "essential epilepsy." Five families were included in which there were similar twins with epilepsy or dysrhythmia. In each pair the fundamental dysrhythmia was the same, although seizures occurred in both twins of only one pair.

The authors stated it to be their belief that the dysrhythmia of epilepsy is inheritable, and that such dysrhythmia may represent a predisposition to epilepsy or some allied disorder. Since 2.4 per cent of the near relatives of the patients had epilepsy and since approximately 60 per cent have dysrhythmia, persons with a predisposition to epilepsy or an allied disorder outnumber actual epilepties about 25 to 1. The incidence of epilepsy is generally stated to be about 0.5 per cent of the population; hence, persons with a predisposition number about 12 per cent of the population.

They felt that these observations should be of value in the prophylaxis and eugenics of epilepsy. The occurrence of dysrhythmia in both parents of an epileptic patient was about thirty-five times the expected chance mating of dysrhythmic persons, suggesting some active selective factor. If a person with epilepsy marries, the authors concluded that his chances of having epileptic children would be decreased should he marry a person with a normal electroencephalogram.

These reports on epilepsy add tremendously to our knowledge of the subject. They show that the physiology of the cortex when it is available for electrical study is aberrant. All observers agree that abnormal potentials occur during overt attacks and that between attacks they may occur. So-called monopolar recording with an indifferent electrode attached to an ear seems to give records typical of epilepsy in a larger proportion of cases, probably a reflection of the fact pointed out by Jasper and Andrews,[37] that such records in some measure are affected by all the potentials generated in the cortex lying between the two electrodes, even although one may be thought of as indifferent. Bipolar recording, as used by Jasper and Hawke,[39] allows records from much more restricted areas of cortex and may not pick up epileptic discharges unless they are very general over the cortex, as in attacks, or unless the electrodes happen to be placed so as to include an area of epileptic discharge between them. All observers agree that the electroencephalographic evidence does not prove the cortical origin of fits in so-called idiopathic epilepsy, and indeed Walter's[74] statements about his findings with collaborators, and Lennox, Gibbs, and Gibbs'[29] contributions strongly suggest some sort of rate-regulating mechanism controlling or coordinating the cortical potentials. Lennox, Gibbs, and Gibbs'[49] data suggest that disturbances of this rate-regulating mechanism may be inheritable, but that some factor, such as injury, may be necessary to precipitate fits on the basis of this fundamental dysrhythmia. Their

report is of the utmost interest, since it attempts on the basis of a large number of records to set up standards of normality, a measure much needed to clarify the whole field of electroencephalography. It should be especially noted that 60 per cent of the near relatives of epilepties have abnormal tracings as compared to their normal standards, but only a small proportion of these individuals have tracings characteristic of epilepsy.

In narcolepsy, according to Walter,[74] the electroencephalogram may show no abnormality, but in many instances a very prominent alpha rhythm from a large focus may be present. The prominent alpha rhythm becomes normal when the sleepiness is controlled by benzedrine. Blake, Gerard, and Kleitman[14] found that tracings from narcolepsy showed the delta activity of sleep at higher levels of consciousness than normal tracings, and that this tendency could be diminished by benzedrine.

Mental deficiencies have been examined by electroencephalography and are generally stated to show no abnormalities. Kreezer,[45] however, reported on a group of mongolian and hereditary mental defects, and found no abnormalities in persons with mental ages above 4 or 5 years of age. Below these mental ages the electroencephalograms were less well organized, showing a good deal of irregular, slow activity and a lesser percentage time alpha than normal (although it is, of course, well known that a moderate percentage of normal persons did not show any alpha rhythm). According to Walter,[74] congenital disabilities such as hemiplegias and diplegias show no abnormality unless associated with convulsions. He felt that this was an illustration of the fact that abnormalities in the electroencephalogram are found only when the cortex is in some intermediate stage of degeneration.

Infections and intoxications have been more or less studied. Jasper stated that in encephalitic processes involving the cortex, abnormal waves in confusing variety might arise, and the results in alcohol and anesthetics suggest that other types of cortical intoxication would give rise to abnormal waves. Jasper and Andrews[37] report such abnormal waves from a case of lead encephalopathy. So far, I am unaware of any study which attempts to differentiate between reversible and irreversible changes in cortical tissue the result of injury of any sort on the basis of electroencephalography. Such a study might well prove useful.

The neuroses are generally stated by various authors to show no abnormality, and Walter[74] states that because of this, epilepsy and hysteria can be successfully differentiated by electroencephalography. Whether behavior problems in children should be classed as neuroses is perhaps a question, but two reports of significant variations in the electroencephalogram in behavior disturbances are available. In 1938 Jasper, Solomon, and Bradley[41] reported electroencephalographic studies in a group of seventy-one children hospitalized because of behavior difficulties, presumed originally to have been psychogenic. They reported definitely abnormal tracings in 59 per cent of the group and probably abnormal tracings in an additional 12 per cent. In 39 per cent of the group the abnormal electrical activity was classified as epileptiform, since it occurred as bursts of waves of large amplitude and slow rate. During a relatively short follow-up period, a number of those who showed epileptiform tracings developed overt epilepsy.

In 1940 Lindsley and Cutts[54] reported from the same clinic on electroencephalographic studies in a group of "constitutionally inferior" and "behavior problem" children. Their material consisted of thirty normal adults (mostly college students), thirty-six normal children between the ages of 7 and 13 years of age, fifty children exhibiting behavior problems, also between 7 and 13 years of age, and twenty-three "constitutionally inferior" children also between 7 and 13 years of age. The records analyzed were taken by the bipolar method from pairs of electrodes over the occipital, central, and frontal regions of each side, the electrodes of each pair being 2.5 cm. apart. Each recording period lasted twenty to forty minutes and ended with a period of hyperventilation lasting one and one-half minutes or less if an "effect" was produced sooner. Using standard samples of record, the records were studied in relation to five frequency bands: 2 to 5 cycles, 5 to 8 cycles, 8 to 12 cycles, 12 to 18 cycles, and 18 to 30 cycles per second. The amplitude, per cent of time each frequency band was present, and number of subjects from each group showing waves in these frequency bands were determined. Such an analysis is very similar to that derived by means of Grass and Gibbs transforms, but much more laborious.

The most striking findings were in relation to the slow frequency bands. The behavior problem group contained two to three times as many children with 2- to 5-per-second waves present at least 10 per cent of the time as did any of the other groups, and both the behavior problem and "constitutionally inferior" groups of children showed a great excess of individuals showing waves in the 5- to 8-per-second band, as compared to the normal adults and children, while the behavior problem group showed a more marked effect in response to hyperventilation than did the other groups. In the frequencies above 8 per second, no significant differences between the various groups were found. The authors conclude that the larger amounts of abnormal, slow waves found in the behavior problem and "constitutionally inferior" group represent disturbances in cortical function which are probably important factors in the causation of behavior problems, tending to prevent easy adjustment to external factors.

This report, interesting and well worked up as it is, again calls attention to the fact that each writer must spend a good deal of time setting up his own standards of reference for the study of his data. Such standards based necessarily on relatively small groups of children are not as satisfactory as those based on larger groups. Some modification of conclusions will be required, no doubt, but Lennox, Gibbs, and Gibbs' data and those presented of the last report should, in the main, withstand such changes without important modification.

Cutts and Jasper[16] reported on the effect of benzedrine and phenobarbital on twelve behavior problem children with abnormal electroencephalograms. The electroencephalograms were designated as epileptoid because of two types of abnormality, the first a well-organized slow rhythm averaging about 6 cycles per second, and the second a poorly organized random tracing with large waves at a rate of 2 to 4 cycles per second prominent in it. Sometimes normal tracings were obtained with bipolar leads from parts of the head and abnormal tracings from others.

Benzedrine improved the clinical behavior of seven of the twelve patients with respect to attention span in school, lessening of over-

activity, and cooperation with the routine of the institution. All those improved had prominent 6-cycle-per-second waves and little or no random activity. The electroencephalograms were not altered.

Phenobarbital made nine of the twelve children worse in respect to increased liability to temper tantrums, impulsive behavior, and irritability. Phenobarbital increased the prominence of the beta rhythm in ten children, but the two who showed no change in the electroencephalogram showed clinical exacerbation, while the three who showed no clinical change all showed increase in the prominence of the beta rhythm. The authors concluded that since benzedrine does not change the electroencephalogram, which is of cortical origin, although it improves the emotional situation, its effect may be on some subcortical neural mechanism.

In this report the ages of the children showing the 6-per-second rhythm is not stated, and the only tracing of the enhanced beta rhythm reproduced might well be produced by activity of voluntary muscle. On the other hand, where normal and abnormal tracings from the same head are shown, the difference between the normal alpha rhythm and the 6-cycle rhythm is obvious.

Stuttering has been studied by Lindsley[53] and by Travis and Knott.[71] Lindsley's data were gathered by means of bipolar records from the occipital and motor speech area, and he concluded that there was a relationship between asynchronism of the alpha rhythm of the two hemispheres or unilateral blocking of the alpha rhythm and episodes of stuttering. Aside from the fact that with the brain exposed, identification of the motor speech area is difficult, no control electroencephalograms of normal speakers during speech are presented. Travis and Knott studied bilateral records from normal speakers and stutterers and concluded that in resting stutterers, there was a greater degree of dissimilarity in the record obtained by bipolar electrodes from the posterior half of the head on each side than in normal speakers. (The difference proved statistically important.) During speech, whether stuttering or not, stutterers tended to show less out-of-phase or dissimilar activity on the two sides than did the normal speakers. It would appear, therefore, that no important abnormality of the electroencephalogram can be demonstrated in stutterers.

A generalized condensation covering all these phases of electroencephalography is extremely difficult. Certain things seem fairly clear. Normal nerve cells can be regarded as bioelectric oscillators, having more or less autonomous periods of their own. In order that they may produce changes in potential sufficiently large to be detectable through the unopened skull, groups of them must apparently work in unison; in the normal individual such synchronization appears largely during the resting state. The potentials recorded from the scalp are apparently generated in the cortex, but the changes occurring during the evolution of sleep, the simultaneous appearance of the K complex over much of the head in response to acoustic stimuli during sleep, and the findings of workers in epilepsy all strongly suggest some rate-regulating mechanism controlling and coordinating the potentials. Studies of energy output by the Fourier transform suggest that a large variety of rhythms are constantly emitted under standard conditions, and that peaks of energy output appear in relation to the most prominent rhythms commonly denoted as alpha and beta rhythms. The

source of the delta waves of sleep and incomplete brain damage remains in doubt. Dusser de Barenne and McCulloch's[21] experiments suggest that they may be a normal product of the lower layers of the cortex. Shift of the energy output beyond certain frequency limits in either direction is accompanied by interference with function, as is also increase in potential of the recorded waves beyond a certain ill-defined maximum.

In clinical medicine the technique of electroencephalography has already proved itself useful in the localization of tumors and other gross injuries involving the cortex. It is also of great use in the diagnosis of epilepsy, where unusual and aberrant cases may be quite baffling. In behavior problems in children, electroencephalography sets apart a group in whom evidence of abnormal physiology exists, but there is some evidence that improvement with drug treatment may take place without any change in the electroencephalogram. Whether spontaneous improvement can occur in any sizable proportion of such cases remains to be seen. Diffuse toxic and inflammatory diseases involving the cortex may be accompanied by abnormal electroencephalograms. As yet no standards are available suggesting that there is any correlation between the electroencephalographic findings and the reversibility of the pathologic changes.

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American Academy of Pediatrics

Proceedings

TENTH ANNUAL MEETING OF THE AMERICAN ACADEMY OF PEDIATRICS

MEMPHIS, TENN., NOV. 18-20, 1940

Round Table Discussion on Infant Feeding

Chairman: Franklin P. Gengenbach, M.D., Denver, Colo.

Associates: Isaac A. Abt., M.D., D.Sc., Chicago, Ill.
Philip F. Barbour, A.M., M.D., Louisville, Ky.
Jay I. Durand, M.D., Seattle, Wash.

Secretary: Harvey Garrison, Jr., M.D., Jackson, Miss.

CHAIRMAN GENGENBACH.—We will not attempt to give a lengthy discussion of any phase of infant feeding, but will give you a chance to ask questions and quiz this board of so-called experts.

Outline used by Dr. Gengenbach:

A. Feeding directions for newborn infant until breast milk appears
   1. Normal presentation and delivery, and average weight.
   2. Prolonged labor, abnormal presentation or delivery.
   3. Mother has been given C.O., quinine, pituitrin, or H.M.C., etc.
   4. Baby is premature or is a congenitally weak and underweight baby.

B. Breast milk
   1. Breasts secrete normally
      a. Interval
      b. Number of nursings
   2. Some milk but insufficient
   3. No breast milk or mother's physician advises against her nursing baby.
   4. Wet nurse
   5. Colic
   6. Vomiting
   7. Constipation
   8. Bowels too loose

C. Bottle feeding
   1. Formula or preparation
   2. Amount
   3. Interval
   4. Vomiting
   5. Colic
   6. Constipation
   7. Diarrhea

D. Accessory foods or vitamins and when started

1. Cod-liver oil
2. Sunbaths
3. Orange juice
4. Cereals
5. Vegetable soups or vegetables

DR. P. F. BARBOUR.—The baby should be put to the breast as soon as it is cleaned up after delivery. The young of practically all animals take the breast soon after they are delivered. Mother Nature has provided something in this way; one should have the baby nurse until the breast milk comes in.

DR. DURAND.—It is very important that the breast be stimulated to establish the proper lacteal flow. Cattlemen have known for a long time that if a calf doesn't get the milk from the cow right at first, it develops a condition known as "scours," which is a bad diarrhea. . . . you are much more likely to establish breast feeding if the rubber nipple is never given to the baby.

CHAIRMAN GENGENBACH.—Is it a good idea to use both breasts at each feeding whether they get very much or not? Demands must be made upon the breast. . . . If the breasts are not emptied, the next time they won't provide so much.

DR. G. W. KUTSCHER, JR., ASHEVILLE, N. C.—Is it advisable to put the baby to the breast for five minutes only the first few nursings in order to avoid cracked nipples?

CHAIRMAN GENGENBACH.—A dry nipple is more apt to crack itself; we put the baby to the breast for five minutes only for two or three times the first day or so.

QUESTION.—Do you do anything to treat the nipple or toughen it before the baby is born? I would like to bring up here for discussion whether it is safe to use boric acid; a saturated solution cakes around the nipple and makes it worse.

DR. O. E. BARBOUR, PEORIA, ILL.—I believe that to take the fingers and pull the nipples very hard is a good procedure, and that during the nursing period the breast should always be dried very thoroughly after nursing. The nipple should be kept as dry as possible during that time.

CHAIRMAN GENGENBACH.—I used to have the mother massage the nipples for a couple of days.

DR. C. E. KITCHENS, TEXARKANA, TEXAS.—I've always told the mothers to wet a brush in the bathtub and massage the nipple during the bath.

CHAIRMAN GENGENBACH.—Thank you very much; I was going to suggest that. Evidently the nipples can stand quite a little punishment.

DR. D. L. SMITH, SPARTANBURG, S. C.—It seems to me that the tight clothing which mothers wear may cause cracked nipples. The breast is pushed back, kept warm and moist, and is in a very good position to develop a cracked nipple. My directions are to wear as little as possible, to loosen the clothing, or to dress like they do on the islands, nothing around the waist and breasts.

DR. E. P. COPELAND, Washington, D. C.—The condition of the nipple itself is a very important thing. We all know that very promising breasts do not work satisfactorily because of cracked nipples. There is no way to insure against such a thing happening. I have always felt that cleansing with castile soap and water was good.

DR. DURAND.—Some of our obstetricians back in Washington refuse to let the baby go to the breast until the breast milk is established.

CHAIRMAN GENGENBACH.—If the mother has received a large amount of narcotic, the baby should not be put to the breast and the breast milk should be expressed and discarded.

At Findelstein's Clinic the wet nurses give 3 or 4 quarts besides nursing their own babies. Does breast feeding make any difference if the baby is premature?

DR. DURAND.—It is best to have breast milk. It is not important to feed the premature infant so frequently. Many of them grow well on the four-hour schedule. These babies do not stimulate the breast well, and if they do not stimulate it enough, the milk may fail.

CHAIRMAN GENGENBACH.—When we borrow breast milk in the hospital we may feed the whole breast milk when it first comes in, but this milk is sometimes quite rich and it may be better to dilute it.

It is best to feed every four hours when the infants are nursing both breasts, rather than to nurse on alternate breasts. At least one-half the milk comes out of the breast in the first five minutes.

DR. O. E. BARBOUR.—Some babies are distended with gas . . . and are relieved by making them belch. In colic, they really suffer from intestinal pain.

DR. P. F. BARBOUR.—Dr. Eugene Roseman brought out the point several years ago that the baby who holds his head back does not have the colic but is hungry. When the child has colic, it is doubled up with the arms across the chest; the knees are drawn up and head pulled forward. In contrast to this, the hungry baby holds his head backward. There is no doubt but that these babies are in pain. Phenobarbital or paregoric may be necessary. A great many colicky babies have no signs of fermentation. Breast milk may have 10 per cent sugar, and a good many samples of milk vary in the quantity of fat. Not only the large fat globules but the variation in size have some influence.

QUESTION.—How do you correct that?

DR. P. F. BARBOUR.—It's a question of the mother's not getting enough rest. The milk may be pumped from the breast, and the fat skimmed off, and there is no further trouble.

More education in our school systems would be very helpful in order that the mothers would know what they are to look forward to.

DR. J. J. HOBSON, MEMPHIS.—What shall we do for the babies who are finally taken off the breast and continue to have colic on formulas?

CHAIRMAN GENGENBACH.—They should be given a sedative. How many use phenobarbital? [Almost all of the men held up their hands.]

DR. P. F. BARBOUR.—It would help to get a complete history of both parents and of their reactions to food. Sometimes the allergic factor of food or their intolerance may explain the colic.

DR. DURAND.—Breast milk is not made up of the food the mother eats, but is made up from the blood supply. An increasing demand on the breast will increase the milk. I think the mother's diet has nothing to do with colic. You can increase the milk more by stimulation of the breast and you can teach the mother to express the milk.

CHAIRMAN GENGENBACH.—In the old days the mothers were told to drink plenty of tea.

DR. RUTH G. ALEMAN, NEW ORLEANS.—Are you pasteurizing the breast milk?

CHAIRMAN GENGENBACH.—It would be wiser to pasteurize it.

DR. DURAND.—Are we going to give vitamin K as a routine measure? Why wouldn't it be a good thing? It can't do the baby any harm.

DR. COPELAND.—I am in favor of using it prophylactically with the mother. I understand that the synthetic preparations are good and that the cost is much lower.

DR. W. C. C. COLE, Detroit.—It is valuable, certainly, in the premature infant and in the abnormal labors. It is not necessary to give bile salts in connection with it since there is no obstruction to the bile passages in the normal baby. It is of no use after the baby has had the hemorrhage. This should be used prophylactically.

DR. R. SPAETH, CHICAGO.—Is it disturbing to an infant with intracranial hemorrhage or other debilitating conditions to feed with a medicine dropper every hour?

DR. COLE.—It is disturbing to feed any baby every hour.

DR. E. E. MOODY, LOS ANGELES.—When do you start training for the movement of bowels? Usually, I instruct the mother to start about the sixth or eighth week by inserting a soap-stick suppository in the rectum and usually establish the habit within a few weeks, and it saves the mother a great deal of difficulty.

CHAIRMAN GENGENBACH.—It isn't a question of whether you're doing anything for the baby; you're doing it for the mother. If you are going to establish the habit, give the suppository after a meal because peristalsis begins then . . . in the intestinal tract.

DR. KUTSCHER.—How many here teach the mothers manual expression? [About 75 per cent held up their hands.]

QUESTION.—What do you do when the mother doesn't have enough breast milk to satisfy the baby?

DR. DURAND.—I try to see that the baby gets the breast milk, with manual expression if necessary. But it doesn't seem very satisfactory in a lot of cases, and if it is too much trouble to keep up the combination feeding, I just take them off the breast. At one time the mortality in the artificially fed baby was six times that of the breast-fed baby.

DR. MOODY.—I'd like to challenge that. We made a survey in Los Angeles and found we had a mortality in the bottle-fed baby three times that of the breast-fed baby.

DR. DURAND.—I do not have such a mortality in the babies that I'm feeding, but in some of the lower social classes like some Mexicans and in large populations as in Los Angeles where the babies are artificially fed, it may be high.

CHAIRMAN GENGENBACH.—I would like to supplement that in a way. We had a baby contest in Denver, and there were over one thousand babies entered. If one judged the babies by weight, height, and size, there was not much difference. Very much to my surprise, I had to give the prize to a bottle-fed baby. Whatever immunity the mother has is given to the baby, to some extent, through her breast milk and this is missed when you are giving the baby something other than breast milk. So, as long as there is some breast milk, I prefer to keep the baby on the

breast. You also get other valuable elements. If it is really necessary to give additional vitamins, you certainly ought to give them to the mother while she is nursing the baby.

QUESTION.—How about the morbidity rate rather than the mortality?

DR. DURAND.—It's a better baby if it's a breast-fed baby. There is some difference.

QUESTION.—Do you think the baby is sick much less over a period of a year's time when he is on the breast rather than the bottle?

DR. DURAND.—Immune bodies probably are not transferred through the milk.

DR. MOODY.—If we talk to these mothers in the first two weeks' time, at least 60 per cent more of them will nurse their babies. We're losing something in building up the stamina of these babies for future life. There isn't another species of animal in the world that borrows milk from other species like we do.

DR. KITCHENS.—How many of you physicians have seen artificially fed babies of the negro race? You don't find many. I have not seen, in about fifteen years of pediatric practice, a negro baby with colic.

QUESTION.—When you can't feed breast milk, what do you prefer to use for the baby?

CHAIRMAN GENGENBACH.—Everything—raw milk, pasteurized milk, sterilized milk, condensed milk. When do you begin artificial feedings, Dr. Cole?

DR. COLE.—I begin the formula on the third day.

DR. ABT.—Do you estimate the calories the baby is getting?

DR. COLE.—No.

DR. J. A. WHEELER, NEWTON, KAN.—How much milk does a baby need to obtain sufficient calcium?

DR. DURAND.—Not too much milk. Some cereals have added calcium.

QUESTION.—There are reports that a large number of older children who have myopia have never taken fat meat; about 80 per cent. I would like to hear your opinion on the use of fats. There ought to be a lot of myopia in Europe right now then.

CHAIRMAN GENGENBACH.—If there is a lack of vitamin A, it might explain the symptoms.

DR. MOODY.—What is the dilution for a 3-week-old baby without enough breast milk?

CHAIRMAN GENGENBACH.—Use about one part evaporated milk to three parts of water.

DR. W. R. SISSON, BOSTON.—In Boston at the Clinic of the Floating Hospital we use properly diluted whole cow's milk. The best substitute for that is evaporated milk with added carbohydrates.

DR. ABT.—I think carbohydrates are necessary to prevent constipation.

DR. DURAND.—It is necessary to have carbohydrates in the proportion of two to one of fat. I have had some trouble with honey producing fermentation.

DR. P. F. BARBOUR.—Some sugars produce more fermentation in some babies, and it is sometimes of value to change from one sugar to another in cases of excess fermentation in the gastrointestinal tract.

DR. DURAND.—It is important that we give them enough food; if we use 7 per cent carbohydrates, and 3½ per cent fat, they will burn and metabolize without trouble if the ratio of two of carbohydrates to one of fat is maintained. How much you dilute the milk depends on how much fluid the baby needs. Two ounces of fluid per pound of body weight is usually required.

CHAIRMAN GENGENBACH.—The other day I was talking with Dr. McCulloch and he gave me a very interesting observation. He said that he was using for normal babies diluted evaporated milk and water without ever any additional sugar or carbohydrates. He said the babies handle it all right. I asked him how much sugar he added, and he said, "I don't add any sugar." I said, "Does that baby ever get constipated?" And he said, "No."

QUESTION.—What accessory foods or vitamins do you use?

CHAIRMAN GENGENBACH.—It doesn't make a great deal of difference about the kind of cod-liver oil; if they take the plain cod-liver oil, all right; and if they don't 5 to 10 drops of the concentrate can be used.

QUESTION.—There has been a loss of about 80 per cent of vitamin B in the cereals put out during the past forty years. What is to be done about this? How are we going to get enough vitamin B in the mother's and child's diet?

DR. ABT.—You can buy all the vitamin that you need at the butcher shop and the grocery store.

CHAIRMAN GENGENBACH.—How many of you give vitamins to the breast-fed baby? [Most of them held up their hands.]

DR. STEWART.—Ordinarily cod-liver oil is valuable also because of its iodine content.

DR. P. F. BARBOUR.—Not many of us have enough experience to evaluate the importance of these vitamins.

CHAIRMAN GENGENBACH.—The other day when we discussed the problems of accessory food, Dr. Stewart of Minneapolis said he didn't believe in giving anything in the bottle. He said: "If you want to keep up breast feeding, give anything else from a spoon. Then when the baby is thirsty, he will turn to the breast." He gave them orange juice and cod-liver oil and in some cases he gave vegetables, and he didn't bother always with canned vegetables. All he did was to see that they were properly cooked, and then just mashed up.

Academy News

Dr. A. Graeme Mitchell of Cincinnati, Chairman of Region III of the Academy, died June 1. Dr. Mitchell was born in 1889 and received his medical degree from the University of Pennsylvania in 1910. After hospital service and study abroad he started the practice of pediatrics in Philadelphia where he remained until 1924 when he was called to the chair of pediatrics at the University of Cincinnati. During the war he served in France and Germany with the A.E.F., leaving service with the rank of Major. At Cincinnati he held with his professorship the associated positions of Director of Pediatrics and Contagious Diseases at the General Hospital, and Chief of Staff and Director of the Children's Hospital. While he was in Cincinnati, the Children's Research Foundation was founded and organized with Dr. Mitchell as Director, and he gathered together and built one of the outstanding departments for pediatric research in the country. He was extremely active in local and national medical organizations and gave unsparingly of his time to further medical and health work for children. He was a member of the American Pediatric Society and served on its Council for a number of years. In 1935 he was Chairman of the Section on Pediatrics of the A.M.A. A founder member of the Academy, he served on many committees and was active on its Executive Committee as a Regional Chairman at the time of his death. With Dr. J. P. Crozer Griffith, he published *Diseases of Infants and Children* in 1927, which appeared in a third edition, revised by Dr. Mitchell, with the title *Textbook of Pediatrics* only a month ago. He was a joint author of a text on pediatric nursing and made numerous other contributions to medical literature. For a number of years he had been on the Editorial Board of the *American Journal of Diseases of Children.*

His untimely death at an age when he was at the height of his activities is a great loss to pediatrics. He had a keen analytical mind and a trenchant wit and method of expression which was fatal to anything that suggested of false or muddy thinking. His lecture, which he was called upon to give many times, entitled "What I Don't Know About the Endocrines," was an example of his honesty of approach to a confused subject which needed debunking. His ready wit, his fund of apt stories, and his personality made him a much sought-after leader in medical meetings, whether it was to conduct a panel discussion on some important phase of medical science, or to preside at a dinner. He had a kindness and fairness in his relations with other men, as all who were associated with him were familiar, and he never used his wit and keenness of mind in an unfair way upon anyone and then only in a sense of fun. He will be missed by everyone who came into contact and association with him. Aside from his never-tiring energy directed to pediatrics, he found time to practice his hobby, an unusual talent for painting and etching. He is survived by his widow, Mrs. Adele Wentz Mitchell, and his twin daughters, Marie Graham and Kathryn Wentz.

At the meeting of Region III held in Chicago on May 15, 16, and 17, there were 664 registrations. Of these, 240, or approximately 60 per cent of the membership of Region III, were members of the Academy. A luncheon was given on Thursday in honor of Dr. Isaac Abt, Dr. Joseph Brennemann, and Dr. Thomas Cooley. The meeting of Region III will be held in Cleveland next year.

The following deaths have recently been reported: Dr. G. W. Kutscher, Jr., of Asheville, N. C.; Dr. Robert G. Sharp of San Diego, Calif.; and Dr. Paul H. Herron, of Oak Ridge, La.

News and Notes

A second edition of the **Directory of Medical Specialists** has been authorized by the Advisory Board for Medical Specialties, to be ready for distribution in February, 1942, with its contents complete to January 1, 1942. It will list the names of approximately 18,000 diplomates of the fifteen American Boards examining candidates for certification in the specialties, including those certified by the American Board of Pediatrics. This is an increase of 4,000 over the first edition issued early in 1940.

The Directory contains a geographic grouping, with data of diplomates revised to date, and in addition, much new information not found in the first edition. Details of formal training is one of these additions, and military appointments now held is another.

Only those who have been formally certified by one of the American Boards can have their names included. There is no charge or obligation for such listings other than certification.

The official nature of this Directory makes it invaluable as a reference book. It may be used generally for referring of patients to distant communities; for information of medical society officers; for gaining detailed knowledge about qualified specialists throughout the United States and Canada; for obtaining detailed information about the American Boards; and for many other purposes.

The first edition had a wide distribution throughout the medical profession as well as medical and other public libraries It is not a commercial undertaking, for the Directory contains no advertising material and is underwritten by the Advisory Board. It actually received subsidizing support so that it could be distributed as near to cost as possible.

Questionnaires for biographic data are now being mailed out with order forms. The secretary of each Board urges that every diplomate return his questionnaire form as quickly as possible, and he is urged also to support this project of the American Boards by his subscription to the Directory. A substantially reduced rate is offered for prepublication orders ($4.75), as the size of the printing is based largely on advance subscriptions.

The publication is issued through the Columbia University Press of New York. The secretary of each American Board serves on the Advisory Editorial Board. Paul Titus, M.D., 1015 Highland Building, Pittsburgh, Pa., of the American Board of Obstetrics and Gynecology, is the directing editor.

At the fifty-third annual meeting of the **American Pediatric Society** at The Homestead, Hot Springs, Va., May 22-24, 1941, the following members were elected officers for 1941-1942: President, Dr. Edwards A. Park, Baltimore; Vice-President, Dr. Joseph B. Bilderback, Portland, Ore.; Secretary-Treasurer, Dr. Hugh McCulloch, St. Louis; Recorder-Editor, Dr. Heyworth N. Sanford, Chicago; and Councilor, Dr. Allan M. Butler, Boston. The following were elected to membership in the Society: Dr. Bruce Chown, Winnipeg; Dr. John A. V. Davies, Boston; Dr. Lee E. Farr, New York; Dr. Stanley Gibson, Chicago; Dr. Harry H. Gordon, New York; Dr. Horace L. Hodes, Baltimore; Dr. Laslo Kajdi, Baltimore; Dr. Waldo E. Nelson, Philadelphia; Dr. Henry G. Poncher, Chicago; Dr. R. R. Struthers, Montreal; and Dr. Josef Warkany, Cincinnati.

The **Society for Pediatric Research** met at Atlantic City on May 5, 1941. The following members were elected as officers: President, Dr. George M. Guest, Cincinnati; Secretary-Treasurer, Dr. Mitchell I. Rubin, Philadelphia.

Book Reviews

Textbook of Pediatrics. J. P. Crozer Griffith and A. Graeme Mitchell. Third edition, 1941, W. B. Saunders Co., Philadelphia. Price $10.00.

Unlike so many "new editions," this is a completely rewritten, revised, and reset edition of Griffith and Mitchell's textbook, even to a change in name. The authors, recognizing that pediatrics is something far more than a discussion of disease, have expanded that portion of the book which has to do with the child by adding new chapters. With the growth of medical knowledge in recent years, it has become impossible for any one or two authors to write critically or authoritatively on all medical subjects. This led to many texts with a number of chapters contributed by individual authors, which in some instances resulted in an unbalanced presentation. In order to avoid this and at the same time bring a certain authority, the authors have submitted to some sixty-odd men, recognized as having particular knowledge in some special field, many of the chapters and subjects for revision and criticism. The text in this way takes full cognizance of the advances in pediatrics during the years subsequent to the previous edition. One striking change in format is the omission of references which followed each subject or chapter in the previous edition (see following review). The revision of a text is a hard, uninteresting task, and the authors are to be complimented in improving the high quality of the previous editions.

Pediatric Bibliography. A. Graeme Mitchell. Monographs of the Society for Research in Child Development, vol. VI, series no. 27, no. 1, National Research Council, Washington, D. C. Price $0.75.

This bibliography, supplementing the new third edition of Griffith and Mitchell's *Textbook of Pediatrics*, is an excellent and most valuable list of references, particularly to articles published in the last decade, which will be of greatest value to anyone who wishes to dig deeper, or to go back to source material, for information beyond that found in the textbook. The references have been most carefully selected, and our thanks are due to both Dr. Mitchell and the Society for Research in Child Development for making this material available to all students and workers in the field of pediatrics.

What Are the Vitamins? Walter H. Eddy, Ph.D. New York, 1941, Reinhold Publishing Co. Price $2.50.

This is a review of our knowledge of vitamins up to December, 1940, based on the author's work and a review of the literature. After discussing vitamins in general and what they do, chapters are given in turn to the properties and functions of the different vitamins—A, B, B_2 or G, P-P, B_6, C, P, D, E, and K. An appendix chapter takes up a consideration of the chemical nature of the vitamins, and another consists of a table of vitamin values.

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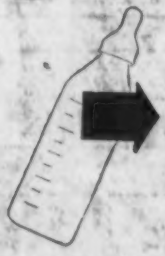

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